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Exploration of Natural Product based Nanostructure Material for Research and Application

TECHNICAL REPORT

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Preface

Madan Bhandari University of Science and Technology Development Board (MBUSTDB) is undertaking preparations for the establishment of a research-oriented world-class university. In this context, MBUSTB is engaging experts for identification of potential areas for research and teaching, which has the potential of directly contributing to economic development of the country.

This publication presents the outcome of a study related to the exploration of natural products-based nano-biomaterials for multidimensional applications, the outcomes of which have the potential of directly contributing to country's economic development. This study is a part of wider studies aimed at exploring the potential of natural products for biomedical, technological and agricultural applications.

MBUSTDB highly appreciates the remarkable hard work and dedication of the author – Dr. Subash Adhikari – for preparing this publication. MBUSTB appreciates and thanks all other individuals and institutions who contributed to bringing out this publication.

Prof. Rajendra Dhoj Joshi
Chairperson
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Executive Summary

This report mainly focuses on the review of natural product and the natural product based nanoformulation for agriculture, biomedical and technological applications, designing of green and efficient procedure for nanostructure synthesis and supporting institutional development activities.

The main content of the report can thus be classified into three different sections.

The first section is the literature review wherein natural product based nanostructures synthesis from forest and agricultural wastes using green synthesis techniques and their application prospective in biomedical, technological and agriculture along with their value chain from source to market products have been presented. The chapters containing this can be outlined as:

1. Review literature to identify natural products including turmeric, rhododendrons, and forest and agricultural wastes, which have potential for synthesis of nano-compounds and nanomaterials.
2. Review literature to identify non-toxic and efficient procedures for synthesis of nano-compounds and nanomaterials from potential natural products.
3. Review literature to identify nano-compounds and nanomaterials from organic sources which have potential for biomedical, technological and agricultural application.
4. Review literature on existing nano-compound/material-based products from organic and organic-inorganic composites for multidimensional use and their value chain from source to products in the market.

The second section of the report contains selection of green and efficient procedures for natural product extraction and nanomaterial synthesis for electrical, optical and agricultural application. The chapters containing this are:

5. Design high gain and efficient procedure for natural product extraction using nanotechnology, among others.
6. Design non-toxic and sustainable procedure for synthesizing nano-compounds and nanomaterials for electrical, optical and agricultural application.

The final section of the report is related to the institutional development activities. The chapters containing this are:

7. Develop national/international collaboration and partnership with institutions/organizations working on nanomaterials/technology based natural product development
8. Explore and identify areas/fields of introduction of nanotechnology for biomedical, technological and agricultural application in relation to the natural products.
9. Formulation of research projects based on nano-technology for development of natural products, including technology development, proto-type development, patenting, production and marketing.
10. Support design of Master's and PhD level course in Madan Bhandari University of Science and Technology (MBUST) for research on natural products of Nepal. Formulation of topics for PhD research and Master's degree research.

In summary, the main content of each chapter can be summarized as:

Identification of natural product based nano-compounds and nanomaterials from forest and agricultural wastes including turmeric and rhododendron are extensively reviewed in Chapter 1.

In Chapter 2 and 3, review of green nanoformulation techniques and identification of green nano-compounds and nanomaterials for biomedical, technological and agricultural applications are presented.

Synthetic and natural product based nanomaterials and nano-compounds for multidimensional usages and their value chain is reviewed in Chapter 4.

Chapter 5 and 6 presents the schemes for green, efficient and high gain natural product extraction and nanoformulation for electrical, optical and agricultural applications.

Similarly, the institutions and organization working in development of natural product based technology employing nanomaterials and nano-compounds for collaborative purposes, various fields within natural product research employing nanotechnology and potential research projects within the field of nano-biotechnology for academic research, product development and marketing are presented in chapters 7-10.

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Introduction

The next generation of technological advancement will mostly comprise of high speed, efficient and miniaturized materials and devices. This comprehensive shift in technology is mainly possible through the modern industrial revolution using nanoscience and nanotechnology.[1, 2] The advantage of having large surface to volume ratio, less material consumption, wide range of materials choices and more efficient performance than their bulk counterpart have provided a valuable alternative to almost all conventional industrial sectors.[3, 4] Some of the sectors using modern nanotechnologies are electronics, medicine, cosmetics, textiles, food science, energy sectors and agriculture. Hence the global nanotechnology industry with market value of 1055 million USD in 2018 is estimated to reach 2223 billion by 2025 [5] showing various new research and development possibilities in wide industrial sectors.

Among various opportunities offered by the advancement of nanotechnology, nano-electronics and nano-optics are some of the key aspects that is driving the next generation electronics and energy based research and applications. Moreover, the growing issues of environment degradation from conventional electronic manufacturing industries and the large amount of unrecyclable electronics waste impacting our resources needs to be addressed seriously.[6] One of the possible solutions to these alarming issues is the use of organic electronic, which offers more eco-friendly and low-cost alternative to current semiconductor technology. The unique properties offered by organic materials like light weight, flexibility, low material consumption and semitransparency are additional advantage compared to silicon based technology.[7] Display devices based on organic-light emitting diodes, organic photovoltaics and organic field-effect transistors are the major application areas of organic materials in addition to light absorbing dyes, electrode materials, charge conductors, color indicators, nanocomposites and neutralizing reagents which are widely used in various modern technologies.[8, 9] These organic materials consists of carbon based small molecules or polymers which are readily available in various naturally occurring plants resources.[10] Moreover, Nepal serves as reservoir of various types of plant resources, especially forest, agricultural and flowering plants that can be utilized in developing products based on organic electronics. Hence either by extracting and engineering the organic compounds and nanomaterials from natural resources or by producing more efficient organic materials through mixing of various extracts and dopants, we can synthesize new organic materials that can have more efficient application in modern electrical, optical and energy storage devices.

Another important aspect of nanotechnology, beyond technological advancement, which will have a profound impact on human development is agriculture industry. Agribusiness is projected to be a 2.9 trillion USD global industry by 2030 and introduction of modern concepts like nanotechnology into conventional agriculture can enhance the possibilities of developing stranded agribusiness with a growth rate of 1.08 billion USD annually.[11] However, the concept of agricultural nanotechnology is still in its early phase and the agriculture industry and its products at present are mainly dependent on the conventional agriculture using inorganic fertilizers and inorganic pesticides. Moreover, the increasing content of inorganic chemicals in the agricultural lands are slowly decreasing the soil quality along with creating human and animal health hazards, mainly due to environment and water pollution.[12] Additionally, the inorganic fertilizer have high nutrient loss through soil and water runoff, low crop yield, emergence of pests, loss of biodiversity and more importantly low nutrient absorption efficiency which thus decreases the plant growth along with increasing the chemical content in soil.[13, 14] To solve these issues, current agricultural industry is rapidly moving towards more sustainable and environment friendly approaches using biologically derived fertilizers and pesticides. At present, 1.4% of the global farmland is using organic farming in fourteen different countries[15] and with innovative research approaches which are environment friendly as well as enhances the nutrients absorptivity in plants, the conventional agriculture can be transformed globally. This can be achieved using natural products based nanofertilizer, nanopesticides and nanoherbicides farming. The design and engineering of nano-biofertilizers with new, green and innovative synthesis techniques can enhance the agricultural productivity since natural product are sustainable, widely available in nature and have very minimal health hazards in living organisms as compared to conventional inorganic fertilizers. Similarly, introduction of nanopesticides and nanoherbicides based on natural product along with nanosensors and smart delivery system for controlled agrochemical release can further boost the agricultural productivity.

Methodology

The methodology used in the report mainly consists of literature review to identify natural products for nanostructure synthesis and applications. For this, various bibliometric sources like Web of Science, Scopus, Endnote, SciFinder and Google Scholar were used. The data sources used in the report were obtained from research papers, review papers, online reports, newspapers and official websites of various academic institutions and industries. The experimental design section in the reports were obtained from conventional protocals provided in the literature and from own research experiences. The Figures provided in the report are obtained from research journals and online reports available in the web. Similarly, some contents in the reports are based on group discussion among experts working in various sections of natural product extraction, organic materials synthesis and their applications.

Chapter 1. Nanomaterials and nano-compounds synthesis from forest and agricultural waste including high value natural products like turmeric and rhodendrons

1.1 Introduction

The wide variety of plants species and their body parts contains various useful products ranging from woods, fruits, manure to raw materials for various industrial products. Besides carbon, the major component of a plant body, there are about 25000 phytochemicals present in colorful parts of the plant bodies which regulates the overall functioning of the plant.[16] These phytochemicals are one of those naturally available chemicals libraries that can be used directly in synthesizing various natural products based medicines, organic compounds based food products and organic fertilizers or indirectly as a component of medicinal, optical, electrical, agricultural and daily wellbeing products. The large class of these plant based chemicals also offer engineering of chemicals/compounds and easy and convenient synthesize of nano-structured compounds and materials. These plant derived nanocompounds and nanomaterials are also the new research avenue in natural product research which is aimed in providing green and organic products in medicine, technology and agriculture fields. In this review, the research trends in synthesizing nanomaterials and nanocompounds from highly potential natural resources like turmeric, rhodendron and other forest and agricultural resources will be discussed.

1.2 Nanocompounds and nanomaterials from Turmeric (Curcuma longa)

1.2.1 Nanocompounds from turmeric

Turmeric, the rhizome with a deep orange-yellowish color is mainly used as a food ingredient besides its other application as a medicinal herb and coloring dyes. Turmeric contains various phytochemicals like terpenoids, curcuminoids, and the products conjugating curcuminoids with monoterpenes, phenolic compounds, flavonoids, saccharides, steroids, fatty acids and alkaloids.[17-19] Among these phytochemicals, curcuminoids accounts to 2-9% of turmeric composition and is the major phytochemical constituent.[20] Till date, about 50 curcuminoids with 3 characteristic subtypes: linearcurcuminoids, cyclic-curcuminoids and curcuminoids conjugated with monoterpenes or sesquiterpenes have been identified. Curcumin, demethoxycurcumin and bis-demethoxycurcumin are the major component of linear curcuminoids out of which, curcumin is the major component which have demonstrated anticancer, antiinflamatory, antioxidative and anti-alzheimer activities in preclinical and clinical studies.[19, 20] Terpenoids including monoterpenoids, sesquiterpenoids, diterpenoids and triterpenoids are another important components in turmeric. Terpenoids are the main constituent of the essential oil in turmeric and researchers have identified about 68 different varieties of terpenoids.[21-23] Similarly, turmeric also contains about 18 different flavonoids and other compounds including phenols, organic acids,steroids, polysaccharides which have been isolated from turmeric in various researches.[21, 24, 25] These various compounds isolated from turmeric have been illustrated in Table 1.

Nano-compounds	**Part of turmeric**	**Phytochemical class**	**Reference**
Demethoxycurcumin	Rhizome	Curcuminoids	[21, 26]
Bisdemethoxycurcumin	Rhizome	Curcuminoids	[21, 26]
Curcumalongin A/B/C	Rhizome	Curcuminoids	[26]
Cyclocurcumin	Rhizome	Curcuminoids	[27]
Bisabolocurcumin ether	Rhizome	Curcuminoids	[28]
Demethoxybisabolocurcumin ether	Rhizome	Curcuminoids	[28]
Didemethoxybisabolocurcumin ether	Rhizome	Curcuminoids	[28]
Terpecurcumin A to Y	Rhizome	Curcuminoids	[28, 29]
(1E,6E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione	Rhizome	Curcuminoids	[26]
(1E,6E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione	Rhizome	Curcuminoids	[26]
1,7-Bis(3,4-dihydroxyphenyl)-1, 6-heptadiene-3,5-dione	Rhizome	Curcuminoids	[26]
(1E,4E)-1-(4-hydroxy-3-methoxyphenyl)-5-(4-hydroxyphenyl)-1,4-pentadien-3-one	Rhizome	Curcuminoids	[30]
1,5-Bis(4-hydroxyphenyl)-1,4-pentadiene-	Rhizome	Curcuminoids	[21, 26]

3-one			
(1E,4E)-1,5-bis(4-hydroxy-3-methoxyphenyl)-penta-1,4-dien-3-one	Rhizome	Curcuminoids	[21, 31]
(1E,4E,6E)-1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one	Rhizome	Curcuminoids	[31]
(4Z,6E)-5-hydroxy-1,7-bis-(4-hydroxyphenyl)-4,6-heptadien-3-one	Rhizome	Curcuminoids	[26]
(4Z,6E)-(+)-1,5-dihydroxy-1,7-bis-(4-hydroxyphenyl)-4,6-heptadien-3-one	Rhizome	Curcuminoids	[26]
(4Z,6E)-(−)-1,5-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-4,6-heptadien-3-one	Rhizome	Curcuminoids	[26]
(4Z,6E)-(+)-1,5-dihydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadien-3-one	Rhizome	Curcuminoids	[26]
(4Z,6E)-1,5-dihydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one	Rhizome	Curcuminoids	[26]
(6E)-(−)-3-hydroxy-1,7-bis (4-hydroxyphenyl)-6-heptene-1,5-dione	Rhizome	Curcuminoids	[26]
(1E,4E,6E)-1,7-bis(4-hydroxyphenyl) hepta-1,4,6-trien-3-one	Rhizome	Curcuminoids	[26]
β-Atlantone	Rhizome	Terpenoids	[21]
Curlone	Rhizome	Terpenoids	[21, 32]
(6R,7R)-bisabolone	Rhizome	Terpenoids	[21]
Bisabolone-9-one	Rhizome	Terpenoids	[21, 32]
Curculonone A to D	Rhizome	Terpenoids	[21]
[1R-[1α(S);4α,5β]]-6-(5-hydroxy-4-methoxy-	Rhizome	Terpenoids	[33]

4-methyl-2-cyclohexen-1-yl)-2-methyl-2-hepten-4-one			
2,5-Dihydroxybisabola-3,10-diene	Rhizome	Terpenoids	[23]
4,5-Dihydroxybisabola-2,10-diene	Rhizome	Terpenoids	[23]
[1S-[1α,2β,5β(R)]]-5-(1,5-dimethyl-4-hexenyl)-2-methyl-3-cyclohexene-1,2-diol	Rhizome	Terpenoids	[33]
[1R-[1α(S);4α]]-6-(4-hydroxy-4-methyl-2-cyclohexen-1-yl)-2-methyl-2-hepten-4-one	Rhizome	Terpenoids	[33]
(6S)-6-[(1R,4S,5S)-4,5-dihydroxy-4-methyl-2-cyclohexen-1-yl]-2-methyl-2-hepten-4-one	Rhizome	Terpenoids	[33]
Bisacurone	Rhizome	Terpenoids	[21]
Bisacurone A to C	Rhizome	Terpenoids	[34]
Ar-turmerol	Rhizome	Terpenoids	[32]
Longpene C and Longpene D	Rhizome	Terpenoids	[35]
Turmeronol A and Turmeronol B	Rhizome	Terpenoids	[32]
Curzerenone	Rhizome	Terpenoids	[35]
Curcumenol	Rhizome	Terpenoids	[35]
(6S)-2-hydroxy-6-(4-hydroxy-3-methylphenyl)-2-methylheptan-4-one	Rhizome	Terpenoids	[36]
(6S)-6-(4-hydroxy-3-methylphenyl)-2-methoxy-2-methylheptan-4-one	Rhizome	Terpenoids	[36]
(6S)-2-methyl-6-(4-formylphenyl)-2-hepten-4-one	Rhizome	Terpenoids	[37]
(1S,6E,10S)-6,10-dimethyl-3-(1-methylethylidene)-11-oxabicyclo[8.1.0]undec-6-en-4-one	Rhizome	Terpenoids	[33]
(6E,10S)-6,10-dimethyl-3-(1-	Rhizome	Terpenoids	[33]

methylethylidene)-6-cyclodecene-1,4-dione			
(2E)-2-[(3E,7E)-4,8-dimethyl-10-oxo-3,7-cyclodecadien-1-ylidene]-propanal	Rhizome	Terpenoids	[33]
(1S,3aS,8aS)-2,3,3a,7,8,8a-hexahydro-1-hydroxy-1,4-dimethyl-7-(1-methylethylidene)-6(1H)-azulenone	Rhizome	Terpenoids	[33]
(1S,3aR,8aS)-octahydro-1-hydroxy-1-methyl-4-methylen -7-(1-methylethylidene)-6(1H)-azulenone	Rhizome	Terpenoids	[33]
(1S,3aS,8aR)-2,3,3a,7,8,8a-hexahydro-1,8a-dihydroxy-1,4-dimethyl-7-(1-methylethylidene)-6(1H)-azulenone	Rhizome	Terpenoids	[33]
Procurcumenol	Rhizome	Terpenoids	[35]
Zedoarondiol	Rhizome	Terpenoids	[21]
Curcumanolide A and Curcumanolide B	Rhizome	Terpenoids	[21]
Longpene A	Rhizome	Terpenoids	[21]
Apigenin	Rhizome	Flavonoids	[38]
Luteolin	Rhizome	Flavonoids	[38]
Apigenin-7-O-β-d-glucopyranoside	Rhizome	Flavonoids	[38]
Luteolin-7-O-β-d-glucopyranoside	Rhizome	Flavonoids	[38]
Luteolin-7-O-(6″-p-hydroxybenzoyl-β-d-glucopyranoside	Rhizome	Flavonoids	[38]
Quercetin-3-O-α-l-rhap-(1→2)-β-d-galactopyranoside	Rhizome	Flavonoids	[39]
Quercetin-3-O-β-d-glucuronide	Leaf	Flavonoids	[39]

Kaempferol-3-O-α-l-rhap-(1→2)-[α-l-rhap-(1→6)]-β-dgalactopyranoside	Leaf	Flavonoids	[39]
Kaempferol-3-O-α-l-rhamnopyranoside	Leaf	Flavonoids	[39]
Dihydroquercetin 7-O-β-d-glucoside	Leaf	Flavonoids	[39]
Myricetin 3-O-β-d-rutinoside	Rhizome	Flavonoids	[40]
6-(4,5-Dihydroxy-4-methyl-cyclohex-2-en-1-yl)-2-hydroxy-2-methylheptan-4-one	Rhizome	Mixed	[41]
Cyclodocosalactone	Rhizome	Mixed	[35]
4-Hydroxybenzaldehyde	Rhizome	Mixed	[42]
Vanillin	Rhizome	Mixed	[21, 42]
p-Hydroxycinnamic acid	Rhizome	Mixed	[24, 43]
Coniferyl aldehyde	Rhizome	Mixed	[24, 43]
3,4-Dihydroxycinnamic acid	Rhizome	Mixed	[24]
(E)-ferulic acid	Rhizome	Mixed	[21, 43]
Dehydrozingerone	Rhizome	Mixed	[21]
3,4-Dimethoxycinnamone	Rhizome	Mixed	[24]
Ethyl ferulate	Rhizome	Mixed	[44]
4-(4-Hydroxyphenyl) butan-2-one	Rhizome	Mixed	[42]
(2R,4R)-6-(4′ -hydroxyphenyl)-hexane-2,4-diol	Rhizome	Mixed	[42]
4″ -(4′ ′ ′ -Hydroxyphenyl-3′ ′ ′ -methoxy)-2″ -oxo-3″ -butenyl-3-(4′ -hydroxyphenyl)-propenoate	Rhizome	Mixed	[37]
2-(2′ -Methyl-1′ -propenyl)-4,6-dimethyl-7-hydroxyquinoline	Rhizome	Mixed	[23]

β-Sitosterol	Rhizome	Mixed	[21]
Daucosterol	Rhizome	Mixed	[44]
Stigmasterol	Rhizome	Mixed	[21]

Table 1: Various nanocompounds isolated from turmeric plants

The composition of the phytochemical contents in the turmeric also depends on the various climatic conditions. Turmeric is native to India and is mainly cultivated in the tropical and subtropical regions of the South and Southeast Asia including India, China and Indonesia. Based on the climatic conditions of these countries the percentage of phytochemical contents also varies as illustrated in Table 2.

Part/condition of Turmeric	**Origin (region)**	**Major compounds and constituent**	**Reference**
Rhizomes	China (Wuning, Jiangxi, Quanzhou, Fujian; Shuangliu, Qianwei, Chongzhou, Sichuan	α-Turmerone 17.27%–31.43%; β-turmerone 14.58%–21.87%; ar-turmerone 7.55%–12.63% (or zingiberene 3.63%–13.19%)	[45]
Rhizomes	Brazil (Mara Rosa)	Ar-turmerone 33.2%, α-turmerone 23.5%, β-turmerone 22.7%	[46]
Rhizomes	Thailand (Isfahan)	γ-Turmerone 68.9%, α-turmerone 20.9%, α-phellandrene 2.2%	[47]
Rhizomes (yellow)	Bangladesh	Ar-turmerone 27.78%, turmerone 17.16%, culone 13.82%	[48]
Rhizomes (red)	Bangladesh	Carvacrol 21.14%, citral 13.91%, methyleugenol 7.31%	[48]
Rhizomes	India (Kanpur)	Ar-turmerone 31.7%, α-turmerone 12.9%, β-turmerone 12.0%	[49]
Rhizomes	India (Orissa)	Ar-turmerone 49.1%, curlone 16.8%, α-phellandrene 5.3%	[50]
Roots	South Korea	α-Turmerone 35.59%, germacrone 19.02%, α-zingiberene 8.74%	[51]
Leaves	South Korea	Terpinolene 71.2%, 1,8-cineole 6.2%, p-cymen-9-ol 4.2%	[52]
Rhizome	Nepal	Monoterpenes 5.58% Sesquiterpenes 84.37% Nonterpenic compounds 8.64%	[53]

Table 2: Turmeric from various parts of the world and their constituents

The various literatures on turmeric and its phytochemical extractions show that more than 700 different compounds have been isolated from turmeric.[54] Among these 32 different Curcuma species have been investigated phytochemically in depth while many other new compounds are still being investigated for various biological and medicinal applications. These turmeric based nano-compounds discovered over a period of 1815-2014 A.D. have been summarized in Figure 1.

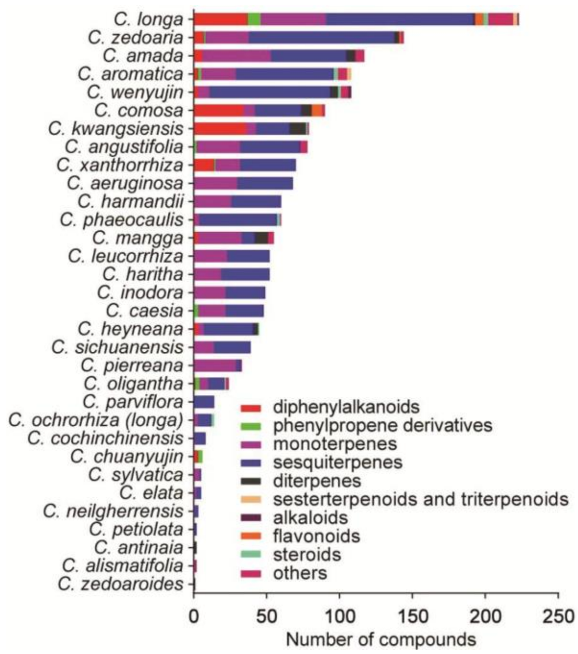


Figure 1: Distribution of various compounds types in Curcuma species. The data were obtained from literature published in 1815-2014. (Adopted from Ref. 42)

Apart from the commonly found orange-yellowish turmeric, there is another perennial herb Curcumin caesia with bluish-black rhizome of the family Zingiberaceae commonly known as black turmeric. This new and less known species in curcuma family has been gradually increasing in popularity because of the various health, medicinal and antibacterial properties. The curcumin caesia as like curcumin longa mostly consists of alkaloids, terpenes, amino acids, carbohydrates, tannins, flavones, flavonoids, steroids, reducing sugar, proteins, anthraquinones, glycosides, cardiac glycosides.[55] Till now about 30 different components have been extracted from black turmeric of which 97.48% are essential oil consisting of camphor, ar-turmerone, ocimene, 1,8cineole, elemene, borneol, bornylavetate and curcumen.[56] Being very rare and unexplored plant species in turmeric family, various application prospective are currently being explored by extraction and identification of new nanocompounds from balck turmeric.

1.2.2 Nanomaterials from turmeric

Reduction in particle size of the active ingredient to nanoparticle size can improve its efficacy, solubility and bioavailability.[57] For the case of curcumin which have low water solubility, poor absorption, low bioactivity and fast metabolism, nano-formulation of curcumin can help enhance the physical and biological activity of curcumin.[58] For example, to increase the rate of dissolution of curcumin, nanocurcumin of particle size 2-40 nm were formed by wet-milling technique.[59] The nanocurcumin with large surface area and having chemical structure similar to that of curcumin had good chemical and physical stability allowing it to be stored in powder form at room temperature and could be freely dispersed in water without the use of any surfactants. It was also found that the aqueous dispersion of nanocurcumin was much more effective than curcumin against various gram-positive and gram-negative bacteria thus proving the importance of nanocurcumin for various antimicrobial activities and applications. Similarly, nanocurcumin prepared by a simple nanoprecipitation technique also showed an improved solubility of curcumin.[57] Nanocurcumin of mean size ~143 nm formed a high-energy amorphous state which could induct intermolecular hydrogen bonding thus enhancing the water solubility as well as drug bonding and release for targeted drug delivery applications. Another mechano-chemical fabrication technique to synthesize uniform nanocurcumin of size range between 100 and 200 nm was developed.[58] In this method the size of the nanocurcumin could be tuned by controlling the flow rate, curcumin concentration in the solution and the sonication time for the nanoparticle preparation which thus allows synthesis of nanocurcumin with varying physical properties that can be used for various biological and pharmacological applications. Besides these biomedical application nanocurcumin has also been investigated for various agricultural application like biocides and biofertilizer for various plants,[60, 61] optical application for fluorescence detection[62] and sensor/probe for detection of trinitrotoluene (TNT) and various other biological species.[63, 64]

1.2.3 Chemical engineering of curcumin and curcumin based nanoformulations

The wide range of phytochemicals and the ease of extraction from turmeric have made this material an important natural product. Moreover, various nano-compounds obtained from the phytochemical extract have been used in clinical and preclinical trials of various human based diseases and in pharmaceutical industries for drug discovery and drug synthesis.[19, 54, 64] Similarly various polymer, liposomes, solid lipid, magnetic, gold and albumin-based nanostructure are extensively used to improve the curcumin based therapeutic applications.[65] Chemical engineering of the nano-compounds obtained from curcumin and synthesis of curcumin analogues nano-compounds is another important research especially in pharmacological applications.

The antioxidant mechanism of curcumin can induce oxygen based radical reaction and thus designing of more effective antioxidative compounds by tailoring the functional groups of curcumin has been possible. Various compounds like 3,5-bis(substituted benzylidene)-4-piperidones II1–16, 2,7-bis(substituted benzylidene)cycloheptanones III1–5, 1,5-bis(substituted phenyl)-1,4-pentadien-3-ones IV1–6, 1,7-bis(substituted phenyl)-1,6-heptadien-3,5-diones V1–6, 1,1-bis-(substituted cinnamoyl)cyclopentanesVI1–6, and cyclohexanesVII1–6 analogous to curcumin derivatives have been developed and evaluated for their anti-oxidative activity.[66] The aqueous solubility of curcumin was improved using cocrystallization of curcumin using salicyclic acid and hydrooxyquinol by intra and intermolecular interaction between the compounds which showed faster powder dissolution rates.[67] This molecular engineering of curcumin could lead to soluble curcumin based drugs and products based on curcumin. Curcumin based light absorber and emitter is another emerging field where curcumin through structural tuning can be used as dye for absorbing broadband light in solar cells and fluorescent material for optical sensors and detectors.[68-71] Similarly, biopolymer using chemically modified curcumin conjugated to polypeptide were created to treat local neuroinflamations,[72] turmeric transformed alkaloid carbon derivatives for activation of nanohybrid organometallic curcumin-aluminium particle for biochemical application[73] and biological reduction using curcumin for the formation of metal particles like gold, silver and curcumin-metal heterostructures like curcumin-gold and curcumin-silver can be prepared for various microbiological applications.[74] The summary of curcumin based application is generalized in the Figure 2.

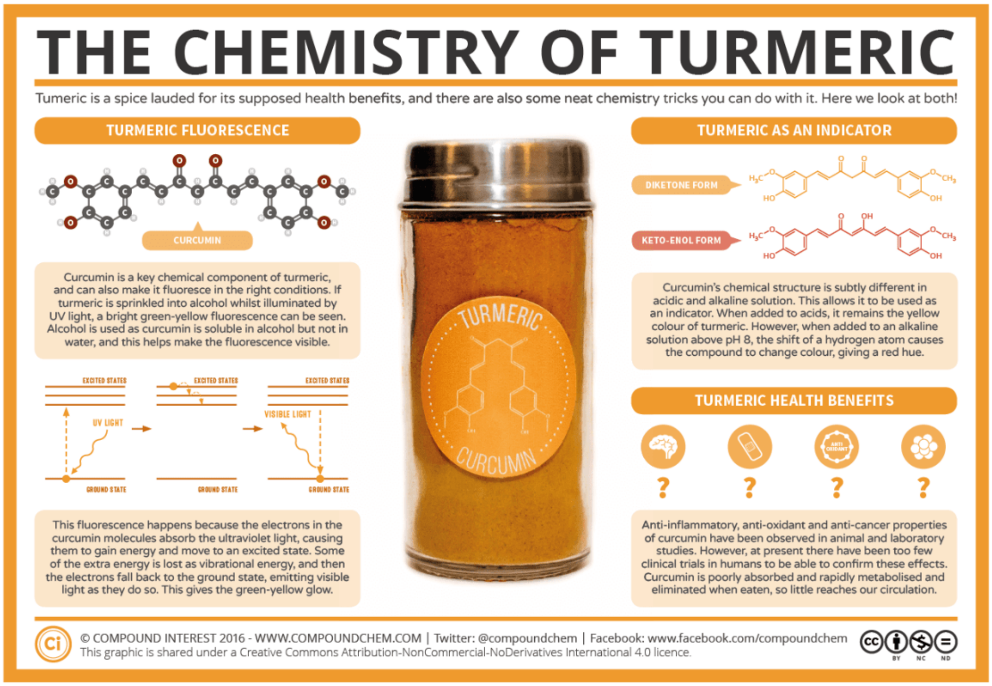


Figure 2: Application prospective of Turmeric Ref: [75]

1.3 Nanocompounds and nanomaterials from Rhododendron

1.3.1 Nano-compounds from rhododendron

Rhododendron is one of those wild flowering plants which have about 1024 natural species with various flowering color.[76] The phytochemical research on various plant species of rhododendron flower have identified various nano-compounds belonging to phenolics, triterpenoid, flavonols, flavonol glycosides and sterols[77] along with ascorbic acid, anthocyanins and various carbohydrate and protein based nano-compounds.[78, 79] These nano-compounds have shown various biological activities like antidiabetic, adaptogenic, antidirraheal, antiinflamatory, antinociceptive, antioxidant, anticancer and antimicrobial along with optical phenomenon mainly as dye for solar light absorption in optoelectronic devices. The flowering part of rhododendron also contains various minerals such as manganese, iron, zinc, copper, nickel, lead and arsenic and these minerals can also be utilized for various biomedical and agricultural applications.[78] Besides the flower, the leaves and bark of rhodendron are also important due to the presence of various phytochemicals like glucoside, ericolin, ursolic acid, quercetin, hyperoside, flavone glycosides and flavonoids in leaves;[80] triterpenoids, ursolic acid acetate, beutulinic acid and leuco-pelargonidin in barks;[81] alkanoids, steroids, terpenoids, anthraquinones, tannins, glycoside saponins and reducing sugar in stem[81] and Alkaloids, terpenoids, tannins, reducing sugars, steroids, saponins, anthraquinones in root of rhododendron plant.[82] Table 3 illustrates some of the nano-compounds found in various plant species of rhododendron.

Nano-compounds	**Rhododendron type**	**Part of rhododendron**	**Phytochemical class**	**Ref.**
Quercetin-3-O-galactoside	R. arboreum	Flower/leaves	Flavonoid	[83, 84]
Quercetin	R. arboreum	Flower/leaves	Flavonoid	[85, 86]
β-Sitosterol	R. arboreum	Leaves	Sterol	[86]
Rutin	R. arboreum	Leaves	Flavonol glycoside	[86]
Quercitrin	R. arboreum	Flower	Flavonol glycoside	[87]
3-O-acetylbetulinic acid	R. arboreum	Bark	Triterpenoid	[88]
β-sitosterol-3-O-beta-Dglucosidose	R. arboreum	Bark	Triterpenoid	[88]
3-β-acetoxyurs-11-en-13 β, 28-olide	R. arboreum	Bark	Triterpenoid	[88, 89]
Betulin	R. arboreum	Bark	Triterpenoid	[88, 89]
Lupeol	R. arboreum	Bark	Triterpenoid	[88, 89]
3-O-acetylursolic acid	R. arboreum	Bark	Triterpenoid	[81]
Betulinic acid	R. arboreum	Bark	Triterpenoid	[81]
Taraxerol	R. arboreum	Bark	Triterpenoid	[81]
Epifriedelinol	R. arboreum	Bark	Triterpenoid	[81]
3,10-Epoxyglutinane	R. arboreum	Bark	Triterpenoid	[81]
Ursolic acid	R. arboreum	Flower/bark/leaves	Pentacyclic triterpenoid	[87, 88, 90]
α- amyrin	R. arboreum	Leaves	Pentacyclic triterpenoid	[90]

β- amyrin	R. arboreum	Leaves	Pentacyclic triterpenoid	[90]
Friedelin	R. arboreum	Leaves	Pentacyclic triterpenoid	[90]
15-oxoursolic acid	R. arboreum	Bark	Pentacyclic triterpenoid	[91]
Arbutin	R. ponticum	Plant	Phenolic glycosides	[92]
Andromedolditerpenes	R. ponticum	Leaves	-	[92]
Acetylandromedienol	R. ponticum	Leaves	-	[92]
Epicatechin	R. ponticum	Leaves	Phenol	[92]
Malvin	R. ponticum	Plant	Anthocyanidin glycosides	[92]
Uvaol	R. ponticum	Leaves	Polyphenols	[92]
3-Methoxypropane-1,2-Diol	R. campanulatum	Leaves	Methoxyphenols	[93]
Beta-Linalool	R. campanulatum	Leaves	-	[93]
Dodecane	R. campanulatum	Leaves	Alkanes	[93]
Alpha-Gurjunene	R. campanulatum	Leaves	-	[93]
7-Isopropenyl-4a-Methyl-1-Methylenedecahydronaphthalene	R. campanulatum	Leaves	-	[93]
Rhodomolleins I/X/XII/XIII	R. molle	Flower	Diterpenes	[94]
Rhodomolins A/B/C	R. molle	Flower	Diterpenes	[95]
1β-rhodomoside	R. molle	Root	Diterpenes	[96]

Secorhodomollolides A/B/C/D	R. molle	Flower	Diterpenes	[97]
2α, 10α-epoxy-3β, 5β, 6β, 14β, 16α-hexahydroxy-grayanane	R. molle	Flower	Diterpenes	[98]
Phloretin 4'-yl-β-D-glucopyranoside	R. molle	Flower	Flavonoids	[99]
7S, 8S-threo-4, 9, 9'-trihydroxy-3, 3'-dimethoxy-8-O-4'-neolignan-7-O-β-glucopyranoside	R. molle	Root	Lignans	[96]
(+)-lyoniresionl	R. molle	Root	Lignans	[96]
(+)-lyoniresionl-3α-O-α-rhamnopyranoside	R. molle	Root	Lignans	[96]
Oleanolic acid	R. molle	Flower	Triterpenes	[100]
Taraxerol	R. molle	Roots	Triterpenes	[101]

Table 3: Nano-compounds extracted from various rhododendron species

1.3.2 Nanoformulations from rhododendron extract

The wide color ranges and various phytochemicals in rhododendron makes it an important plant species that can be utilized for various compound synthesis and also as a secondary component in various biomedical and daily wellbeing products. There are two main areas where rhododendron is being used for product development and research. One of the main research areas is utilization of the color component in this materials for synthesis of natural dyes. Similarly, biogenic synthesis of various nanomaterials is another emerging are which is being viewed as an alternative to physical and chemical based nanomaterial synthesis.

The natural pigments like tannin, anthocyanin, betalain, chlorophyll and carotenoids present in flower, leaves and fruits are one of the natural sources of organic compounds and dyes that can be used in various optical and solar energy harvesting devices.[102-106] As compared to chemically synthesized dyes, these natural organic compounds and dyes can be synthesized by low cost and environment friendly techniques which makes it a commercial product that has high scope for large scale application.[107] These nano-compounds can be easily bonded with various metal and compounds structures which thus allow fabrication of hybrid optical and optoelectronic devices. For the case of rhododendron, two natural pigment, anthocyanin and carotenoid have been extracted from the flower of rhododendron species with different colors. The anthocyanin based natural dyes from pink, red and violet rhododendron flowers used in dye-sensitized solar cell (DSSC) could produce a solar conversion efficiency of 0.33 and 0.27% with high fill factor of around 72%.[107] The carotenoid extract from rhododendron however can boost the efficiency to 0.57% primarily because of the condensation of alcoholic-bound protons with the metal oxide structure in the DSSCs.[108]

Biogenic synthesis of various metal-based nanoparticles using natural product extract is one of the emerging research especially in pharmaceutical and biomedical fields.[109] Among various plant species used for the nanoparticle synthesis, rhododendron is also one of the choices especially for silver and metal-oxide nanoparticles synthesis. For example, the leaves extract of Rhododendron ponticum produced were used as a source of reducing and stabilizing agent for the synthesis of silver nanoparticles of size around 10-21 nm.[110] Silver nanoparticles with size distribution of 25-40 nm were also synthesized by flower extract of Rhododendron dauricum through biological reduction.[111] Similarly, leaves extract of Rhododendron arboreum and Rhododendron arboreum can also be used for the green synthesis of calcium oxide and magnesium oxide nanoparticles.[112] Apart from this, to assess the cellular mineral uptake and for oxidative stability, a nanoscale gum Arabic stabilized Rhododendron arboreum flower extract emulsion was formulated.[113] The nanoemulsion were reproducible, cost-effective and stable showing remarkable potential for emerging functional food and enteral nutrition with effective storage and oxidative stability. Additionally, the nanoemulsion system also has potential to encapsulate and protect micronutrients, bioactive compounds and drugs.

1.4 Nano-compounds and nanomaterials from forest and agricultural wastes

Pharmaceutical, biomedical and optical applications are the major research areas that are currently using the nano-compounds and nanomaterials from various forest and agricultural products. Primarily, the phytochemical extracts from forest and agricultural products are used as the oxidizing and reducing agents during the synthesis of metal-based nanomaterials and nano-compounds and as natural dyes in various optical and coloring based applications. The table below illustrates various nano-compounds and nanomaterials obtained from forest and agricultural extracts.

Plant source	Nano-compounds extracted from plant sources	Nanoparticle synthesized from nano-compounds	Ref.
Eucalyptus camaldulensis (Masala)	Methanol	Au	[114]
Avena sativa (oat)	Amino, Sulfhydryl and carboxylic group	Au	[115]
Cinnamomum camphora (Camphor) (leaf)	polyol components and the water-soluble heterocyclic components	Au and Ag	[116]
Pelargonium graveolens (leaf)	Terpenoids	Au	[117]
Azadirachta indica (Neem)	Reducing sugar and/or Terpenoids	Au, Ag and Au core-Ag shell	[118]
Aloe vera	Carbonyl compounds	Au and Ag	[119]
Acalypha indica	Quercetin, plant pigment	Au and Ag	[120]
Cassia fistula (Raj Brichhya)	Hydroxyl group in plant extract	Au	[121]
Mirabilis jalapa (Sandhyamalati)	Polysaccharides	Au	[122]
Trigonella-foenum graecum (Fenugreek)	Flavonoids	Au	[123]
Mentha piperita	Menthol	Au and Ag	[124]

Alternanthera sessilis (Stalkless Joyweed)	Amine, carboxyl group	Ag	[125]
Citrullus colocynthis (Bitter apple)	Polyphenols	Ag	[126]
Andrographis paniculata (Titkaa)	Alkaloids, flavonoids	Ag	[127]
Boswellia serrata	Protein, enzyme	Ag	[128]
Caria papaya	Hydroxyl flavones, catechins	Ag	[129]
Dioscorea bulbifera (Gittha)	Diosgenin, ascorbic acid	Ag	[130]
Euphorbia prostrata	Protein, polyphenols	Ag	[131]
Gelsemium sempervirens (Jasmine)	Protein, amide, amine group	Ag	[132]
H. canadensis	Phenolics, protein	Ag	[133]
Tinospora cordifolia (Gurjo)	Phenolic compound	Ag	[134]
Diospyros kaki (Haluwabed)		Bimetallic Au/Ag	[135]
Aloe vera	Biomolecules	In2O3	[136]
Cinnamon zeylanicum (Dalchini)	Terpenoids	Pd	[137]
Gardenia jasminoides Ellis	geniposide, chlorogenic acid, crocins and crocetin	Pd	[138]
Cinnamomum camphora	Polyols and heterocyclic components	Pd	[139]
Medicago sativa (Alfala)		Ti-Ni alloy	[140]
Medicago sativa (Alfala)	galic acid reduction into radical tannins	FeO	[141]
Dodonaea viscosa (Alar)	Flavonoids, tannins and saponins	Fe, Cu and Ag	[142]
Adathoda vasica	vasicine or quinazoline alkaloids	Fe2O3 and Ag/Fe2O3 composite	[143]
Physalis alkekengi	Chlorophyllin	ZnO	[144]
Sedum alfredii Hance	Chlorophyll	ZnO	[145]
Taraxacum officinale (Dandelion)	Flavonoids and phenolics	CoO	[146]
Celosia argentea	Functional groups in bioactive compounds	Co	[147]

Table 4: List of various nano-compounds extracted from forest and agricultural products and the bio-nanomaterials synthesized from the biological extract mainly for pharmaceuticals and biomedical applications

Plant source	**Nano-compounds and nanomaterial based dyes extracted from plant sources**	**Ref.**
Black rice	Anthocyanin	[148]
Erythrina Variegata	Carotenoid, Chlorophyll	[148]
Rosa xanthina	Anthocyanin	[148]
Kelp	Chlorophyll	[148]
Capsicum	Carotenoid	[148]
Mangosteen pericarp	a-Mangostin/b-mangostin/rutin	[103]
Hibiscus sabdariffa L	Cyanidin-3-glycosides/delphinidin-3-glycoside	[149]
Beta vulgaris rubra	Betalains	[150]
Bixa orellana L	Bixin	[151]
Spinach	Modified chlorophyll/neoxanthin/violaxanthin/lutein	[152]
Calafate	Delphinidin	[153]
Jaboticaba skin	Peonidin	[153]
Gardenia fruit	Crocetin/crocin	[154]
Red Sicilian orange ‘‘Moro’’	Cyanin	[155]
Eggplant skin	Nasunin	[155]
Prickly pear	Betaxanthin	[156]
Tradescantia Zebrina	Anthocyanin	[157]

Kapok	Antocyanin/carotenoid	[157]
Canarium odontophyllum	Anthocyanin	[158]
C. odontophyllum + Ixora sp	Anthocyanin	[158]
China loropetal	Chlorophyll	[148]
China redbud	Chlorophyll	[148]
Mangosteen pericarp	cyanidin-3-sophoroside/cyanidin-3-glucoside	[159]
Achiote seed	Carotenoid bixin/carotenoid norbixin	[160]
Chrysanthemum	Xanthophyl	[161]
Halymenia agardhii	Chlorophyll	[162]
Terminalia bellirica(gaertn)roxb/Ceriops tagal/Maclura cochinensis	Phenolic compounds	[163]
Mangosteen pericarp	Anthocyanin	[108]
Phaseolus vulgaris L. (Kidney beans)	Anthocyanin (cyanidin 3,5-diglucoside, delphinidin 3-glucoside, cyanidin 3-glucoside, petunidin 3-glucoside and pelargonidin 3-glucoside)	[164]
Bauhinia (Bauhinia purpurea) and Kalanchoe (Kalanchoe blossfeldiana) flowers	Anthocyanin	[164]
Cape honeysuckle (Tecomaria Capensis) flowers	β-Carotene	[165]
Spinach leaves	Chlorophyll	[166]
Betroots	Betalain	[166]
Shiso leaves	Sshisonin/chlorophyll	[167]
Pomegranate fruits	Cyanin	[168]
Brassica Oleracea	Anthocyanin	[169]
Red-perilla	Shisonin	[170]
Jack fruits (Artocarpus heterophyllus Lam)	Morin	[171]
Onion Skin (Allium cepa)	pelargonidin (5,5,7,4 tetrahydroxy antocyanidol)	[171]

Hina leaves (Lawsonia inermis L)	Hennotannic acid	[171]
Indigo seed (Indigofera tinctoria)	Indigotin	[171]
Rubia roots (Rubia tinctorum)	Alizarin	[171]
Tea wastes (Camellia sinensis)	Catechins	[171]
Saffron (Crocus sativus)	Pelargonidin	[171]
Bog blueberry fruits (Vaccinium uliginosum L.)	Anthocyanin	[172]
Grapes	Anthocyanins	[173]

Table 5: List of various nano-compounds and nanomaterials based dyes extracted from forest and agricultural products

1.5 Research trends in natural product based nano-compounds and nanomaterials synthesis in Nepal

There are around 6391 flowering plant species in Nepal with a global share of 2.76% that has been used for energy, construction, flavored species and medicines.[174] However, this large natural resource in Nepal has negligible contribution in national economy. Utilization of various components of these plants for high value medicinal, daily wellbeing, technological and agricultural products through large scale industries are yet to be initiated in Nepal. Instead, low to high value plant species and natural products from these plants are exported in raw quantities. Moreover, some of the plant species like rhododendron and orchid are abundantly available in various parts of Nepal. Nepal possesses 30 various color species of Rhodendron and 57 species of Orchid that are founds in various parts of Nepal.[175, 176] Similarly, various natural compounds like phenolics, alkaloids, terpenoids and sterols can be found in many of the forest and agricultural products in Nepal.[177] Hence there are various research opportunities within the large variety of plant species in Nepal especially for initiating pharmaceutical, biomedical and dye based industries within Nepal.

Turmeric is one of those high prospective plant species that is largely utilized in natural medicines and optical products. The quality of turmeric has higher significance in Nepal because it is being grown from higher altitude of the Himalayan region to the lowlands in Terai within 4325 hectors of land and thus have uniqueness in flavor, aroma, and phytochemical contents.[178] Turmeric grown in various parts of the country contains more than 75 nano-compounds and 98.59% of which are found to be essential oils.[53] The essential oil contains 15 monoterpenes (5.58%), 43 sesquiterpenes (84.37%) and 10 nonterpenic components (8.64%). The major constituents were ß-turmeron, a-turmeron, Epi-a-patschutene, ß-sesquiphellandrene, 1,4-dimethyl-2-isobutylbenzene, (±)-dihydro-ar-turmerone, zingiberene, E-a-atlantone and (-)-caryophyllene oxide. Nano-compounds obtained from Nepalese Turmeric and their contents are illustrated in Figure 3.

Name	GC %	Name	GC %	Name	GC %
1,8-cineole	0.10	(*E*)-*β*-farnesene	1.04	1,7,7-trimethylbicyclo[2.2.1]hept-2-yl-3-methyl-2-butenoate	1.40
a-?-dimethylstyrene	0.08	*β*-cedrene	0.38	*β*- tumerone	17.74
Linalool	0.15	*a*-humulene	0.81	Epi-*a*-patschulene	3.52
1,8-menthadien-4-ol	0.15	*a*-copaene	0.14	*a*-tumerone	8.19
?-cymen-8-ol	0.83	1-(1,5-dimethyl-4-hexenyl)-4-methyl- Benzene	3.80	Spathulenol	0.42
Azulene	0.16	*β*-cedrene	0.40	Neocurdione	0.83
a-terpineol	0.08	Zingiberene	4.03	Curcumenol	1.51
4-(1-methylethyl)-benzaldehyde	0.86	Dihydroarylcurcumen	0.89	(6*R*,1'*R*)-6-(1',5'-dimethylhex-4'-enyl)-3-methylcyclohex-2-enone	1.79
2-caren-10-al	0.24	*β*-bisabolene	2.30	(-)-neocloven-(II)	0.70
4-vinylguaiacol	0.11	3,5,7,7-tetramethylcycloocta-2,4-dien-1-one	0.27	1-[1-bromo-2-ethyl-3-methylcycloprop-1-yl]cyclopent-2-en-1-ol	0.67
2-cyclohexen-1-one, 3-methyl-6-(1-methylethylidene)	0.19	*β*-sesquiphellandrene	4.99	Artemisia ketone	0.64
d-elemene	0.18	*a*-patchoulene	0.81	Atlantone	3.06
3-allyl-6-methoxyphenol	0.26	Sesquisabinene hydrate	0.26	*β*-ionol	0.22
Aristolen	0.11	*β*-cedrene	1.14	Atlantone	0.11
4-methyl-4-phenyl-2-pentanone	0.24	Nerolidol *E*-farnesol	1.48	Allyl ionone	0.14
a-cedrol	0.48	1-(1,2,3-trimethyl-cyclopent-2-enyl-ethanone.	1.14	Artemisia ketone	0.70
β-elemene	0.81	4,5,9,10-dehydro-isolongifolene	0.31	Ledenoxide-(I)	0.38
7-epi-sesquithujene	0.47	*ar*-tumerone	0.83	2,6,10-trimethylundecan-(5Z)-2,5,9-trien-4-one	0.07
β-patchoulene	0.88	2,3-dibromo-8-phenyl-*p*-menthane	2.39	2-methyl-1-phenyl-3-(?-tolyl)-1,3-propandiol	0.13
(-)-aristolene	0.28	(-)-caryophyllene oxide	3.09	? -elemene	1.14
trans-caryophyllene	1.95	1,4-dimethyl-2-(2-methylpropyl)-Benzene,	4.40	Guaia-3,9-dien	0.17
(±)-dihydro-*ar*-turmerone	4.27	Tricyclo[2.2.1.0(2,6)]heptane, 1,7-dimethyl-7-(4-methyl-3-pentenyl)	3.52	*β*-humulen	0.09
Epi-*a*-patschulene	3.67			Total	98.59

Figure 3: Constituents and contents of various nano-compounds found in Nepalese Turmeric (Adopted from Ref. 41)

Another important plant species that have high research potential in Nepal is Rhododendron. Research on various species of Rhododendron found in different regions of Nepal have identified existing and new nano-compounds. Among the Rhododendron varieties, Rhodendron Lepidotum found in high Himalayan regions is expected to have high medicinal values and also possess some new and unidentified nano-compounds. To identify the phytochemical contents, Rhodendron Lepidotum were collected from Langtang region of Nepal at an altitude of 3800 m.[179] The biological extract of this Rhodendron Lepidotum identified four triterpenoids; lupeol acetate, lupeol, β-sitosterol, ursolic acid and oleanolic acid and one disaccharide called β-D-fructofuranosyl-α-Dglucopyranoside apart from other commonly found phytochemical like carbonyl, carboxylic carbonyl, acetoxyl carbonyls and ester carbonyl groups. Among these compounds, β-sitosterol was reported for the first time in Rhodendron Lepidotum. Similarly, Rhododendron arboreum (Smith) collected from Palpa district of Nepal at an altitude of 1350 m showed presence of alkaloids, flavonoids, coumarins and saponins.[180] The nano-compounds extracted consists of Rhodolatouside A, Rhodolatouside B, Coumaric acid, Gallic acid, Rhodolatouside A, Leuco-pelargonidin, Rhodolatouside B, Myricetin, Hyperoside, Quercetin, Maslinic Acid, Linoleic acid, 1-Naphthalenepropanol, Octadecanoic acid, and Betulinic Acid/Ursolic acid of which Rhodolatouside A and Rhodolatouside B were reported for the first time from Nepal.

Similarly, research works on natural dye extraction for the prospective application in DSSC and organic light emitting diodes have also been initiated in Nepal. The flower and leaves extract of Berberis aristata, Bougainvillea glabra, Calendula officinalis, Callistemon citrinus, Capsicum annuum, Chrysanthemum indicum, Curcuma Angustifolia, Dacus carota, Euphorbia pulcherrima, Gomphrena globosa, Lawsonia interrnis, Malvaviscus arboreus, Myrica nagi, Nyctanthes arbor-tristis and Punica granatum were used for the preparation of various dye samples.[181] These dye sample were thus characterized using optical spectroscopy to understand their absorption and fluorescence properties and find their prospective for application as light absorber in solar cells and light emitting diodes. Furthermore, Hibiscus-rosa-sinensis, Cysanthemum (Marigold), brassica nigra (Mustard), Tagetes erecta (Godawari) and Terminalia arjuna were also used for the biological extraction of natural dyes.[182] The obtained natural dyes were compared with various other synthetic dyes to find the prospective of using low cost and organic materials for various optical and opto-electronic applications.

These natural product based research are mostly carried out as academic research project. There are few local products like pickle, juice, jam, oil, wine and briquettes that are made in household level within the Nepalese communities using turmeric and rhododendron.[183, 184] These products are mostly consumed within the local levels and there are no any industries as such that are targeted for commercializing these products. Until now, the common industrial practice in Nepal is to sell raw form of natural products. Powder form of turmeric as a spice product and the essential oil is the only known natural product based commercial product in Nepal.[185] However there is no any specific grading and guideline of the natural product for export purpose. Hence one of the major area that MBUST can facilitate in utilizing the natural product is commercializing these local product through research and education.

1.6 Prospective

The demand of medicinal, biomedical and technological products will continue to grow with the increase in human population and the human needs. Majority of these product requirements is being fulfilled by chemically synthesized materials and compounds. However, the adverse effect of these chemical products is being observed in human health and the environment. Hence as a substitute, green and cost effective materials from natural sources are on the rise. For this, numerous phytochemicals available in forest and agricultural byproducts have been explored and the application prospective of these natural compounds are growing. Moreover, the low quantity of phytochemical obtained from the natural products are still a major concern. For this, synthesis of nano-compounds and nanomaterials from the low quantity of natural products and the phytochemicals obtained from the plant sources can fulfill the global. It is because nano-compounds and nanomaterials are known to consume low material quantity and also enhance the material performance and surface area within the nanoscale regime. Hence there are various research possibilities within the nanoscale region that are being explored globally in order to substitute synthetic materials. Nepal should also initiate such high value and modern research in order to compete with the global research trend and also outmost utilize its diverse natural resources. However, the main research prospective in Nepal at present is to identify various nano-compounds present in varieties of plant species while the application based research of these nano-compounds identified in Nepal is still not deemed priority. This has thus motivated entrepreneurs to export the raw natural products rather than initiating industries based on natural products. Similarly, there is a huge prospective of nanoparticle based research in the global pharmaceutical and electronic/opto-electronic research and Nepal still lacks fundamental research in the field of nanotechnology and nano-biotechnology. Promotion of these high value nano-based research can open several research and industrial prospective within Nepal.

Chapter 2. Utilization of non-toxic and efficient procedure for nanomaterials and nano-compounds synthesis from natural products

2.1 Introduction

Nature is an abundant source of biological, physical and chemical materials for sustaining and developing life forms. The elemental and chemical matters contents found in the natural has also inspired human to develop various tools and techniques in the field of science, technology and human development. Among these, plant and its constituents are of the largest resource that not only provide food and air but are also one of the largest sources of chemical and biological matter for industry and research. However, the industrial utilization of natural products depends on the availability of forest and agricultural waste. With the growing human population and the human needs in various sectors of lives, the natural product resource utilization has to be balanced. Hence one of the newly developed research trend is to utilize the nanostructure form of these biological resources for various industrial applications. Nanostructure which have large surface to volume ratio, ability to bind with various other materials, low material consumption and superior performance than its bulk counterpart have shown various new possibilities in the field of health, technology developments, energy devices and agricultural productivity. [186]

Out of many nano-compound and nanomaterial synthesis procedure, physical and chemical synthesis methods like physical vapor deposition, chemical vapor deposition, sol-gel and colloidal methods are currently commercialized for large scale synthesis (see Figure 4).[187] Moreover, the high cost required in the material synthesis, toxicity of the synthetic material and the synthesis procedure along with the environmental issues arising due to toxicity have led to the development of biological synthesis method using green chemistry approach.[188] In this review, we will present various no-toxic and efficient nano-compound and nanomaterial synthesis procedures which have high prospective for applications.

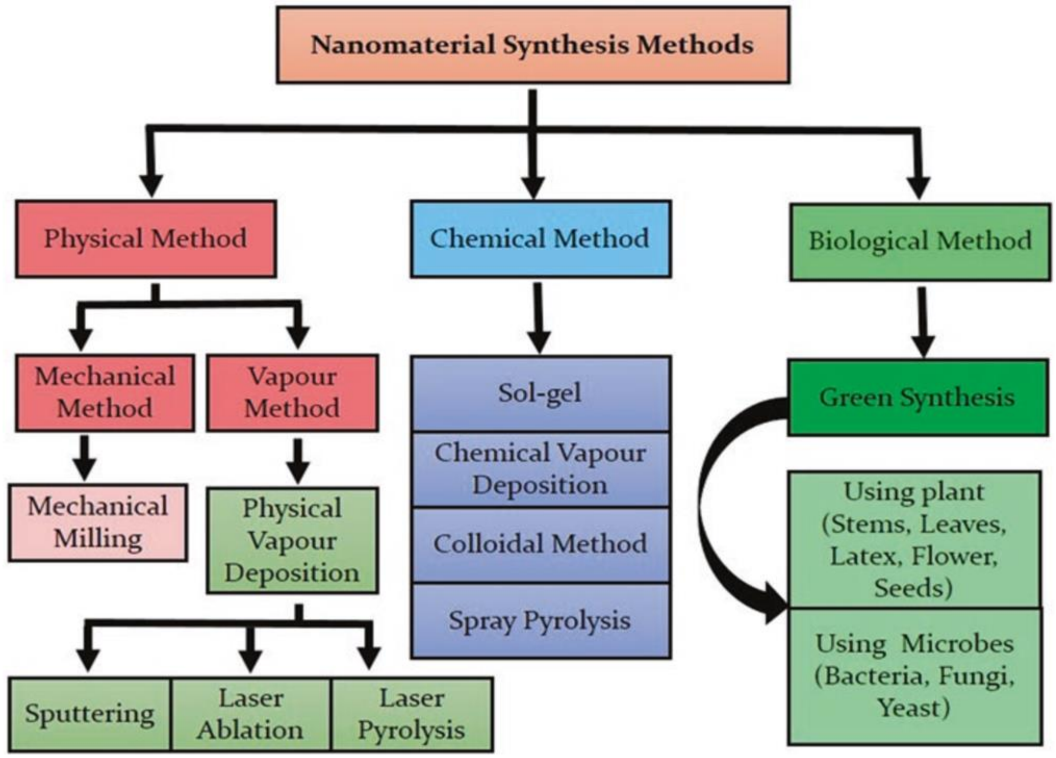


Figure 4. Synthesis methods for nanomaterials (Adopted from Ref. 2)

2.2 Nanostructures and nano-compound synthesis from physical and chemical methods

Various nanomaterial synthesis procedures described in Fgure 4 has their individual significance and drawbacks. The physical methods is preferred when high quality and uniform film thickness are required while chemical methods are used when large quantity of low cost material needs to be synthesized. The major drawbacks of physical method is high cost of material and the synthesis system while chemical synthesis methods products huge chemical waste in the environment and also the materials are mostly toxic to human and animal health.[189] The drawbacks of both these nanomaterial synthesis procedure can be compensated by the biological method using natural products as this follows a green synthesis techniques that can also reduce the cost of material and the synthesis system as well as produces highly efficient materials for various biological, pharmaceuticals and biomedical applications. These various nanomaterials synthesis schemes using natural products are explained below, especially focusing on the high efficiency and non-toxic material synthesis procedures.

In both chemical and physical method, top-down and bottom-up techniques are the usual synthesis procedure to synthesis nanomateirals and thin films.[190, 191] Top-down is a deformation of bulk material to make fragments and nanostructures and bottom up technique is assembly of atom and molecules to make nanostructure and thin films. In the top-down approach mechanical grinding or milling is one of the cost effective and green techniques to synthesis large scale nanomaterials. Coconut shell nanoparticles with size distribution of 50-120 nm were synthesized using planetary mill and ceramic ball.[192] Cellulose nanocrystals and nanofibers synthesized using ball milling and chemical synthesis using organic compounds are another important green and cost effective nanoformulation techniques using biological resources.[193, 194] The plant derived cellulose materials have large scale application in paper, textiles, coatings, pharmaceuticals, implants and tissue engineering. Cellulose resources are also the source of various carbon nanostructure which can be synthesized using external head or pressure thus using a non-chemical green synthesis technique.[195]

Besides nano-cellulose structures synthesis, nanocurcumin and the techniques required for the nanocurcumin synthesis is one of the largely explored research area at present. Various nanocurcumin synthesis techniques like coacervation, nanoprecipitation, spray drying, single emulsion, solvent evaporation, microemulsion, wet milling, thin film hydration, solid dispersion, emulsion, polymerization, fessi, ionic gelation, ultrasonication and anti-solvent precipitation can be used.[196-199] Among these, coacervation techniques usages organic solvent dissolution, suspension and centrifugation; spray drying usages mini spray dryers to spray curcumin nano-suspension;[200] wet-milling by dispersing curcumin in water under ultrasonication and centrifugation;[201] thin film hydration using organic solvent mixing, sonication, evaporation and centrifugation;[202] emulsion polymerization of organic solvent dissolution, ultrasonication and precipitation[203] and ultrasonication by organic solvent dissolution are some green and cost effective techniques used in the nanocurcumin synthesis.[204] Beside these techniques, the chemical synthesis of nanocurcumin using organic solvents like dichloromethane and water to obtain perfectly spherical, crystalline and uniform nanocurcumin of diameter around 100-200 nm[58] and using polyvinylpyrrolidone polymer and ethanol to obtain nanoprecipitated nanocurcumin of mean particle diameter around 143 nm are some of the green nanocurcumin synthesis techniques.[57] Other synthesis techniques using green chemical approaches like supercritical liquid, ionic liquid, microwave and thermal decomposition of plant and phytochemical extracts are used as an additive techniques in biological nanostructure and nano-compound synthesis.[205]

2.3 Nanostructures and nano-compound synthesis from biological methods

Biological synthesis of nanomaterials and nano-compounds are considered green synthesis as they use natural resources for the nanostructure and nano-compound synthesis. There are various biological synthesis techniques using plant extract and microorganisms that are currently used in research as well as industrial production of nanomaterials and nano-compounds. Also the scalability, bio-compatibility and nanoparticle synthesis using universal solvent like water are some of the important advantages that biological synthesis offers. The various nanomaterial and nanocompound synthesis methods using biological resources are described below.

2.3.1 Algae based nanomaterial synthesis

The enzymes and functional groups in the cell wall of algae can be used for reducing the metal ions into nanostructure forms (see Figure 2).[206] They hyper-accumulate heavy metal ions and have capability to remodel them into more malleable forms. Algae based nanoparticles synthesis is green biosynthesis procedure where algae extract can be prepared in water or in organic solvents by simple heating or boiling. This algae extract which consists of carbohydrates, proteins, minerals, fats, fatty acids and some bioactive compounds like polyphenols and tocopherols can thus be incubated with the ionic metallic compounds under conditions like stirring, heat or pressure for the reduction of metal ions into nanostructure forms.[207] Cyanobacteria and eukaryotic like, L. majuscule, S. subsalsa, R. hieroglyphics, C. vulgaris, C. prolifera, P. pavonica, S. Platensis and S. fluitans have been commonly used for the algae based nanomaterial synthesis.[208] Various nanomaterials of gold, silver, palladium, platinum, iron, cadmium, titanium oxides, zinc oxides and the biometallic nanostructures can be synthesized using algae extracts.[207, 209, 210]

2.3.2 Bacteria based nanomaterial synthesis

Prokaryotic and actinomycetes bacteria have been commonly used in biosynthesis of metal and metal-oxide nanoparticles such as gold, silver, lead, platinum, copper, iron, cadmium and their oxides.[211-216] The bacteria based biosynthesis mainly occurs through the cell wall of bacteria through interaction of chemically reactive groups in the metal containing solution (see Figure 2). The cell wall contains a large number of metal binding sites and the mechanism of metal reduction occurs either through intracellular or extracellular process.[217] Various bacteria are known to produce naomaterial of various size and morphology which have application mostly in the agriculture, medicinal, cosmetic and drug industries.[211, 217]

2.3.3 Fungi and yeast based nanomaterial synthesis

Fungi are one of the most important microorganism for the biological nanomaterial synthesis as they can form well defined size and morphology of nanoparticles.[211] Also there are about 5.1 million species of fungi on earth and many of them offer potential for extracellular or intracellular synthesis of nanomaterials. Due to the presence of inter-cellular enzymes, fungi can act as a biological agent for synthesis of nanoparticles.[218] In the intracellular process, metal ions are attached to fungal cell surfaces via electrostatic interactions and the enzymes in the fungal cell wall can reduce the metal ions ions into metallic nanoparticles. Similarly in the extracellular synthesis, the enzymes in the cytoplasm are responsible for the metal ion reduction. The fungi metabolites are responsible for reducing toxic metal ions to nontoxic metallic nanoparticles form through the catalytic effect of extracellular enzymes.[219] Some examples of nanomaterial synthesis using fungi are the formation of silver nanoparticles using Fusarium oxysporum,[220] gold nanoparticle using Candida albicans,[221] platinum nanoparticle using Fusarium oxyporum,[222] zinc oxide nanoparticle using Aspergillus strain[223] and titanium oxide nanoparticle using Aspergillus flavus.[224]

As like other microorganism, yeast can also be used for the biosynthesis of nanomaterials. The chemical species can be biologically reduced through the cell wall absorption in yeast. [225, 226] There are about 1500 yeast species and yeast species commonly used for the synthesis of various metallic and semiconductor nanomaterials. Some example of yeast based nanomaterial synthesis are gold and silver nanoparticles through Saccharimyces cerevisae broth [226] and cadmium sulfides semiconductor nanocrystal using Candida glabrata and Schizosaccharomyces pombe and lead sulphide nanocrystals using Torulopsis sp.[211] The schematic for the fungi and yeast based bioreduction is shown in Figure 5.

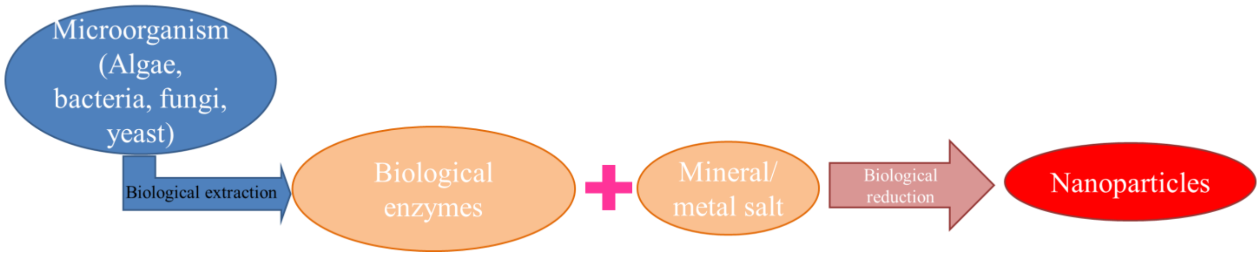


Figure 5. Schematic diagram for the synthesis of nanomaterials using microbes

2.3.4 Plants based nanomaterial synthesis

As like enzymes in microorganism, plant contains phytochemicals which can be conveniently extracted using green synthesis to obtain various bioactive compounds as shown in Figure 6.[227] These bioactive compounds can thus be used for biological reduction of mineral/metal salts for synthesis of various nanomaterials. The process has been shown schematically in Figure 7. The extremely short reaction time for biological extraction as well as biological reduction, low toxicity and the in-situ stabilization of the nanomaterials during reduction process are additional advantage of plant based nanomaterial synthesis as compared to physical and chemical synthesis methods.[228-230] In plant based nanomaterial synthesis, the bioreducing and stabilizing ability of an extract is likely linked to its phytochemical content, i.e., its phenolics, flavonoids, phenolic acid, terpenoids, vitamins, glycosides, polysaccharides, organic acids, and proteins. Phenolics are polyhydroxy water-soluble plant secondary metabolites consisting of cinnamoyl and benzoyl systems. The antioxidant potential of flavonoids and their free hydrogen, liberated during keto-enol conversion, are supposed factors involved in the fabrication of metallic nanoparticles. [23–25] Another category of phenolics, involved in the biosynthesis of nanostructures, are the phenolic acids that contain a phenolic ring and an organic carboxylic acid function. Biosynthesis of nanostructures using these phytochemicals is linked to the metal-chelating ability of the highly nucleophilic aromatic rings of phenolic acids, determining their antioxidant ability. Similarly, for the case of the proteinmediated bioreduction process, nanoparticles can bind to proteins through their free amino or carboxylate groups. Amino acids, as the monomers of proteins, have an ability to reduce and bind to metal ions. This may represent a mechanism for bioreduction, binding metals on the surface of proteins using chelation and proton transformations for the formation of nanomaterials [35–37].

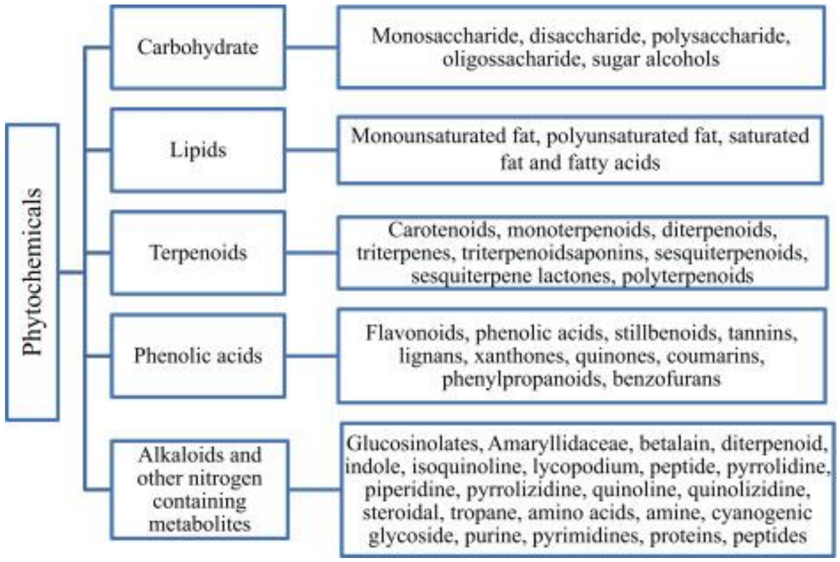


Figure 6. Categorization of phytochemicals obtained from various biological sources (Adopted from Ref. 32)

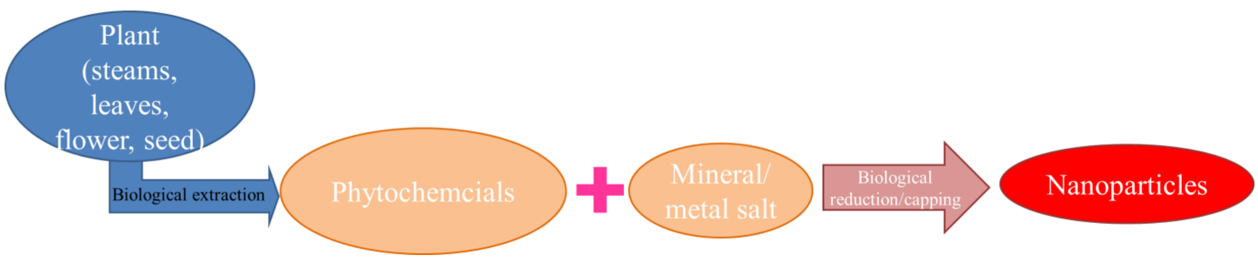


Figure 7. Schematic diagram for the synthesis of nanomaterials using plants

These biologically synthesized green nanomaterials can be applied in biomedical and organic agriculture fields. For the case of biomedical research, bio-nanomaterials can either be used in medicines, targeted drug delivery, nano-biosensor and disease research.[230-232] While for the case of agriculture, bio-nanomaterials and nanocompounds can be used as organic fertilizer, organic pesticides, nanoherbicides along with its application in nanosensors and smart delivery system for controlled agrochemical release.[233, 234] This is thus possible with wide variety of bio-nanomaterials like gold, silver, iron, platinum, copper, titanium, zinc, magnesium, titanium di-oxide, zinc oxide and magnesium oxide, iron oxide and their heterostructure synthesized from various plant species like Eucalyptus camaldulensis (Masala),[114] Avena sativa (oat),[115] Dioscorea bulbifera (Gittha),[130] Azadirachta indica (Neem),[118], Dodonaea viscosa (Alar),[142] Cinnamon zeylanicum (Dalchini),[137] Medicago sativa (Alfala), [140] Physalis alkekengi,[144] and Taraxacum officinale.[146] The nanomaterial synthesis using plant extracts thus covers various material choices ranging from metallic to semiconducting and magnetic bio-nanomaterials. Moreover, these bio-nanomaterials have large application potential in electronic/optical devices, biomedical sensors/equipment and additionally as a micronutrient supplement to plants.

2.4 Prospective in Nepal

The nano-compound and nanomaterial synthesis is also gaining popularity in Nepal with the availability of research funding and research infrastructure development from government and private sectors. The natural product based drugs and daily wellbeing product manufacturers for various non-chronic diseases are the common industries within Nepal that usages traditional milling methods and phytochemical extraction to synthesis powder and liquid form of raw natural products. Similarly there are government and private industries which produces essential oils like chamomile oil, rosin, turpentine oil, lemon grass, citronella and others which can be used for the purpose of making medicinal and well-being products. These phytochemical can be obtained using the natural product extraction techniques. However, most of these industries in Nepal are non-regulated and the details synthesis procedures are mostly unknown. Moreover, these products are consumed by large Nepalese population as a daily immune-booster drug or as disease preventive drugs. Since there are not known side effects, it supports the hypothesis that these drugs are mostly obtained through natural synthesis techniques using biological extraction using water or organic chemicals or dry milling and crushing techniques.

2.5 Conclusion

The biological resources for the synthesis of nanomaterials and nanocompounds are abundant in the nature. Also the various synthesis techniques that can be used for nanomaterials fabrication with specific size and morphology are additional advantage that the biosynthesis allows. However, various external parameters like mixing ratio, temperature, pH, incubation period and aeration are factors that has to be optimized in physical, chemical, microorganism or plant based biosynthesis procedures (see Figure 8).[235] Moreover, the advantage of having biologically stabilized nanomaterials, choices of nanomaterials from metallic, semiconducting, metal oxide and the mixed structure, cost effective procedure and the ability to reduce the biological extract using universal solvent like water makes the biosynthesis procedure more preferred as compared to the chemically synthesized nanomaterials.

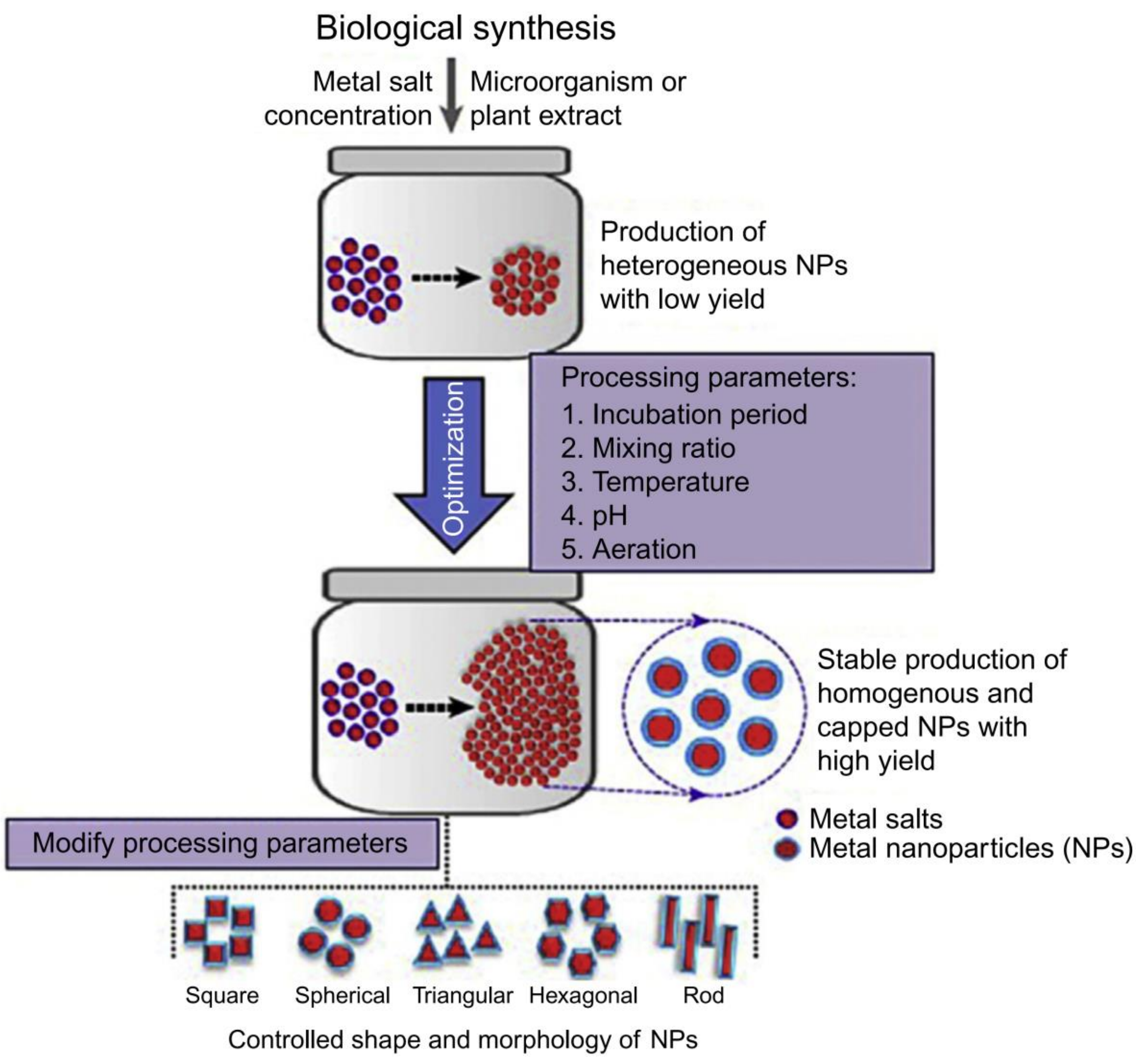


Figure 8. Procedure for biological synthesis of nanomaterials using microorganism and plants (Adopted from Ref. 61)

Chapter 3. Organic nanomaterials and nano-compounds for biomedical, technological and agricultural application

3.1 Introduction

Commercial nano-compounds and nanomaterial can be synthesized using various techniques as described in Figure 4. Among these synthesis methods, biological synthesis using plants and microbes can produce convenient and cost effective green bio-nanomaterials and nano-compounds which are more advantageous in terms of toxicity and in vivo use in human and animal as compared to physical and chemically synthesized nano-compounds and nanomaterials. Additionally, bio-nanomaterials can be synthesized in large scale due to the abundantly available plant and microbes resources. More importantly, the bio-nanomaterials are stabilized in-situ during growth which thus ensures the long term stability of these bio-nanomaterials and nano-compounds.[229] These properties have thus generated new research trend with commercial prospective in medical and health research, organic agriculture and cost effective and green electrical, optical, catalytic and energy production/storage devices (see Figure 9).

Plant and microbes contains phytochemicals which can be conveniently extracted using green synthesis to obtain various bioactive compounds (Figure 6).[227] These bioactive compounds can thus be used for synthesis and engineering of various organic nano-compounds. For example, natural resources like pea flower, red cabbage, red-perialla, pomegranate fruit, shiso leaf, indoline, spinach leaves, beetroot extract and rhododendron contains naturally available pigments such as anthocyanins, carotenoids and chlorophyll which can thus be used in synthesis of optical dye for use in dye-sensitized solar cells.[107, 108, 149, 166, 170, 236-238] Similarly, ruberene, tetracene, pentacene, tetracyanoquinodimethane are the major carbon based polymer or pi-conjugated molecules and polyaniline, polypyrrole, poly(benzobisimidazobenzophenanthroline) are nanostructure conjugated polymers and co-polymers which are used in organic field effect transistors, organic light emitting diodes and energy storage devices.[239-243]

Figure 9. Application areas of green nanotechnology (Adopted from Ref. 2)

Furthermore, the biological compounds extracted from plant and microbe using green synthesis method can be used for the biological reduction of mineral/metal salts for synthesis of various nanomaterials (see Figure 10). The large scale availability of these biological resources can thus provide cost effective and commercial scale nanomaterials for multifunctional use. More importantly, the extremely short reaction time for biological extraction as well as biological reduction, low toxicity and the in-situ stabilization of the nanomaterials during reduction process are additional advantage of plant and microbe based nanomaterial synthesis as compared to physical and chemical synthesis methods.[228-230] Hence, these biologically synthesized green nanomaterials can be applied in biomedical and organic agriculture fields. For the case of biomedical research, bio-nanomaterials can either be used in medicines, targeted drug delivery, nano-biosensor and disease research.[230-232] While for the case of agriculture, bio-nanomaterials and nanocompounds can be used as organic fertilizer, organic pesticides, nanoherbicides along with its application in nanosensors and smart delivery system for controlled agrochemical release.[233, 234] This is thus possible with wide variety of bio-nanomaterials like gold, silver, iron, platinum, copper, titanium, zinc, magnesium, titanium di-oxide, zinc oxide and magnesium oxide, iron oxide which covers various material choices ranging from metallic to semiconducting and magnetic bio-nanomaterials. Moreover, these bio-nanomaterials can be used as electronic/optical devices, biomedical sensors/equipment and additionally as a micronutrient supplement to plants.

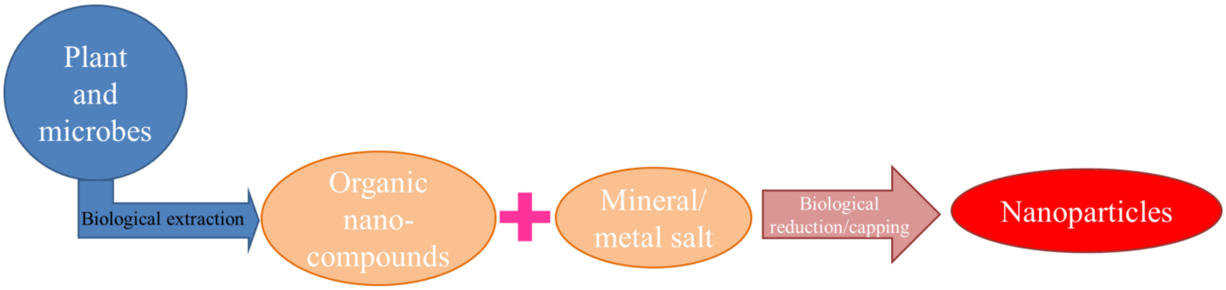


Figure 10. Schematic diagram for the synthesis of nanomaterials using plant and microbes

3.2 List of various bio-nanomaterials synthesized from various plant resources based biological reducing agent and its potential application area

Nanoparticle	**Plant used**	**Biological extract**	**Characteristics**	**Potential application areas**	**Ref.**	**Remarks**
Au	Eucalyptus camaldulensis (Masala)	Methanol	5.5 nm	Antimicrobial	[114]	Spherical nanoparticle
Au	Avena sativa (oat)	Amino, Sulfhydryl and carboxylic group	10-40 nm	Antimicrobial	[115]	Various shapes, Au(III) to Au(0)
Au and Ag	Cinnamomum camphora (Camphor) (leaf)	polyol components and the water-soluble heterocyclic components	Ag (55-80 nm) Au (15-25 nm)	Antimicrobial and antiviral	[116]	Stabilized nanoparticles
Au	Pelargonium graveolens (leaf)	Terpenoids	10-50 nm	Biosensor/ drug delivery	[117]	Particle and rod
Au, Ag and Au core-Ag shell	Azadirachta indica (Neem)	Reducing sugar and/or Terpenoids	Ag: 5-35 nm, Au: traingular Ag-ASu: 50-100 nm	Antimicrobial/anticancer/biosensors	[118]	Flavanone and terpenoid are for stabilization

Au and Ag	Aloe vera	Carbonyl compounds	10-30 nm spherical and 50-350 nm traingles	Biosensor/ drug delivery	[119]	Spherical and triangular
Au and Ag	Acalypha indica	Quercetin, plant pigment	20-30 nm	Antibacteri al	[120]	Spherical
Au	Cassia fistula (Raj Brichhya)	Hydroxyl group in plant extract	55-98 nm	Antihypogl ycemic	[121]	Spherical
Au	Mirabilis jalapa (Sandhya malati)	Polysacchari des	~100 nm	Antimicro bial	[122]	Spherical
Au	Trigonella -foenum graecum (Fenugree k)	Flavonoids	15-25 nm	Catalytic	[123]	Spherical
Au and Ag	Mentha piperita	Menthol	90-150 nm	Antibacteri al	[124]	Spherical
Ag	Alternant hera sessilis (Stalkless Joyweed)	Amine, carboxyl group	40 nm	Antioxidan t, antimicrob ial	[125]	Spherical
Ag	Citrullus colocynthi s (Bitter apple)	Polyphenols	5-70 nm	Antioxidan t, anticancer	[126]	Triangle
Ag	Androgra phis paniculata (Titkaa)	Alkaloids, flavonoids	67-8 nm	Hepatocur ative activity	[127]	Spherical
Ag	Boswellia serrata	Protein, enzyme	7-10 nm	Antimicro bial	[128]	Spherical
Ag	Caria papaya	Hydroxyl flavones, catechins	15 nm	Antimicro bial	[129]	Spherical
Ag	Dioscorea bulbifera (Gittha)	Diosgenin, ascorbic acid	8-20 nm	Antimicro bial	[130]	Rod and traingular
Ag	Euphorbia prostrata	Protein, polyphenols	~52 nm	Antiplasm odial	[131]	Rod and spherical

Ag	Gelsemium sempervirens (Jasmine)	Protein, amide, amine group	~112 nm	Cytotoxicity	[132]	Spherical
Ag	H. canadensis	Phenolics, protein	~113 nm	Cytotoxicity	[133]	Spherical
Ag	Tinospora cordifolia (Gurjo)	Phenolic compound	~34 nm	Antilarvicidal	[134]	Spherical
Bimetallic Au/Ag	Diospyros kaki (Haluwabed)		50-500 nm		[135]	Cubic
In2O3	Aloe vera	Biomolecules	5-50 nm	Optical activity	[136]	Spherical
Pd	Cinnamon zeylanicum (Dalchini)	Terpenoids	15-20 nm	-	[137]	Spherical
Pd	Gardenia jasminoides Ellis	geniposide, chlorogenic acid, crocins and crocetin	3-5 nm	Catalyst	[138]	Stabilized spherical nanoparticles
Pd	Cinnamomum camphora	Polyols and heterocyclic components	3.2-6 nm	Biocatalyst	[139]	Spherical
Ti-Ni alloy	Medicago sativa (Alfala)		1-4 nm	-	[140]	Spherical with core shell structure
FeO	Medicago sativa (Alfala)	galic acid reduction into radical tannins	2-10 nm	Magnetic devices/molecular imaging	[141]	Spherical
Fe, Cu and Ag	Dodonaea viscosa (Alar)	Flavonoids, tannins and saponins	~27, 29 and 16 nm	Antimicrobial activity	[142]	Stabilized spherical nanoparticles
Fe2O3 and Ag/Fe2O3 composite	Adathoda vasica	vasicine or quinazoline alkaloids	6-22 nm	antibacterial, antifungal and anticancer properties	[143]	Stable spherical nanoparticles
ZnO	Physalis alkekengi	Chlorophyllin	~72.5 nm	Cosmetic/ Optical	[144]	Spherical

				and electronic devices		
ZnO	Sedum alfredii Hance	Chlorophyll	~53.7 nm	Cosmetic/ Optical and electronic devices	[145]	Spherical
CoO	Taraxacum officinale (Dandelion)	Flavonoids and phenolics	50-100 nm	Catalyst	[146]	Stabilized spherical nanoparticles
Co	Celosia argentea	Functional groups in bioactive compounds	-	Antioxidant, Antibacterial, Hemolytic and Catalytical Agent	[147]	Stabilized nanoparticles

Table 6: Nanomaterials synthesized using plants based biological extract for various applications

3.3 List of various bio-nanomaterials synthesized from various fungus sources (mushroom) based biological reducing agent and its potential application area

Nanoparticle	Mushroom used	Biological extract used for bio-reduction and nanomaterial capping/stabilizing)	Potential application	Reference
Ag	*Pleurotus florida*	Riboflavin	Antibacterial	[244]
Ag	*Microporus xanthopus*	Functional group of aldehydes, alcohol and carboxylic acid	Antibacterial	[245]
Ag	*Volvariella volvacea*	Carboxylate ion group of amino acid	Antioxidant and antimicrobial	[246]

Au	*Volvariella volvacea*	Free amino groups	Plasmonics	[246]
Se	*Pleurotus tuber-regium*	Polysaccharides protein complexes	Cancer chemoprevention	[247-249]
Pd	*Mixed mushroom sources*	Carboxylic acid, Protein functional groups	Biocatalyst	[250]
Cd	*Coriolus versicolor*	carboxyl, amino, and thiol groups	Antimicrobial and energy based devices	[251]
CdS	*Pleurotus ostreatus*	Polypeptides	Optical devices	[252]
ZnS	*Agaricus bisporus*	Protein derivatives and amide groups of protein	Nanotuned device	[253, 254]

Table 7: Nanomaterials synthesized using fungus based biological extract for various applications

3.4 Prospective

The biologically synthesized nano-compounds and nanomaterials can be controlled in crystallinity and morphology (shape size size) through temperature, pH and concentration of the biological extract.[255-257] These biologically synthesized organic nano-compounds offers light weight, flexibility, low material consumption, semi-transparency, low cost and eco-friendly alternative as compared to current silicon based technology.[258] Furthermore, the possibilities to engineer these organic nano-compounds can provide additional advantage in replacing various existing synthetic materials in medicines, electronic, optical, energy storage/production devices. Similarly, the vast library of biosynthesized nanomaterials can be compiled in the form of nanofertilizer to support plant growth, enhance root-shoot functionality, increase chlorophyll content, enhance the soil quality and regulate the primary and secondary nutrient to enhance the nutrient content in the plant resources.[259-261] Additionally, many of the metallic and semiconducting nanomaterials have antimicrobial, antiviral, anticancer, antiplasmodial and antifungal properties which can be used in various commercial medicines, targeted drug delivery and biomedical research fields.[230, 244, 247, 262] Furthermore, metallic, semiconducting and magnetic nanomaterials have further possibilities in fabrication of efficient biosensors, medical imaging devices, bio- catalytic agents, cosmetics and optical and electronic devices.

Chapter 4. Organic and organic-inorganic composite based nanomaterials and nano-compounds for multidimensional use and their value chain from source to market products

4.1 Introduction

The need of efficient and convenient human lifestyle has induced new and innovative research in fields of food, agriculture, technology, construction, transportation, environment and health.[263] These modern research areas are possible with the use of new and more efficient materials and the technology that are developed to make the products and designs more convenient and economic. For example, the traditional means of transportation running with coal engines are slowly being replaced by highly efficient and environment friendly electrical vehicles running with batteries or hydrogen and solar energies.[264, 265] Similarly, the traditional silicon based photovoltaic devices and catalytic devices using rare materials like Platinum are slowly being replaced with nanomaterials and nanotechnology.[266, 267] Moreover, the rise of nanomaterials and nanotechnology have replaced almost all the traditional industries ranging from electronic, optics, energy storage/production, pharmaceuticals, cosmetics to agriculture and food production, processing and safety.[268, 269] Hence, shifting with the global industrial trend of producing nanomaterials and nanocompounds and technologies based on these has been important for countries and industries so as to maintain the economic growth.

At present the global nanotechnology market is worth 75.8 billion USD which mainly comprises industries related to electronic, sporting goods, automotive, energy storage, aerospace, defence, food and pharmaceutical.[270, 271] The majority of these industries usages silver nanoparticles, nanocomposites, quantum dots, nanoclays, nanofibers and nanoscale ceramic powder.[268] Moreover, the global nanomaterial market consists of various classes of nanomaterials ranging from metal and non-metal to its oxides, nanomaterials of various dimensions (0D/1D/2D) and nanoclays and nanocellulose.[272, 273] Among these metal and non-metal oxide based nanomaterials are most widely applied in the industrial production while other nanomaterials and nanocompounds are also slowly moving from research to global nanotechnology industry.

Moreover, the major factors restraining the development of global nanotechnology market from its rise in early 2000 are toxicity of nanomaterial on human health and environment and stringent requirements of the government bodies on adopting the nanomaterials and nanotechnology in commercial products.[268, 274, 275] However with the extensive research on toxicity, stability and wide scale applicability of various nanomaterials, nanocompounds and nanocomposites, these low dimensional materials have found industrial application either as a final product or as an additive supplement to existing industrial products.[276] Besides these, the new trend of producing large scale commercial nanomaterials and nanocompounds from natural sources are another important development for the direct use of nanomaterials in human bodies as well as in health and environment based application where chemically synthesized nanomaterials are restricted.[277]

4.2 Global scenario of nanotechnology market

The global market for nanomaterials can be segmented into three different classes: a) metal and non-metal oxides, metals and alloys, dendrimers, nanoclay and nanocellulose; b) nanoparticles, nanofibers, nanotubes, nanowires and c) carbon black, carbon nanotubes, graphene, fullerene and other carbon based nanomaterials.[268, 278, 279] These nanomaterials are mostly obtained through material engineering process involving various chemical synthesis techniques.[280] Moreover, most of these nanomaterials can also be obtained through natural resources using green synthesis techniques.[281] These synthesis technique mostly depends on the application purpose, material stability and the chemical toxicity of the nanomaterials.

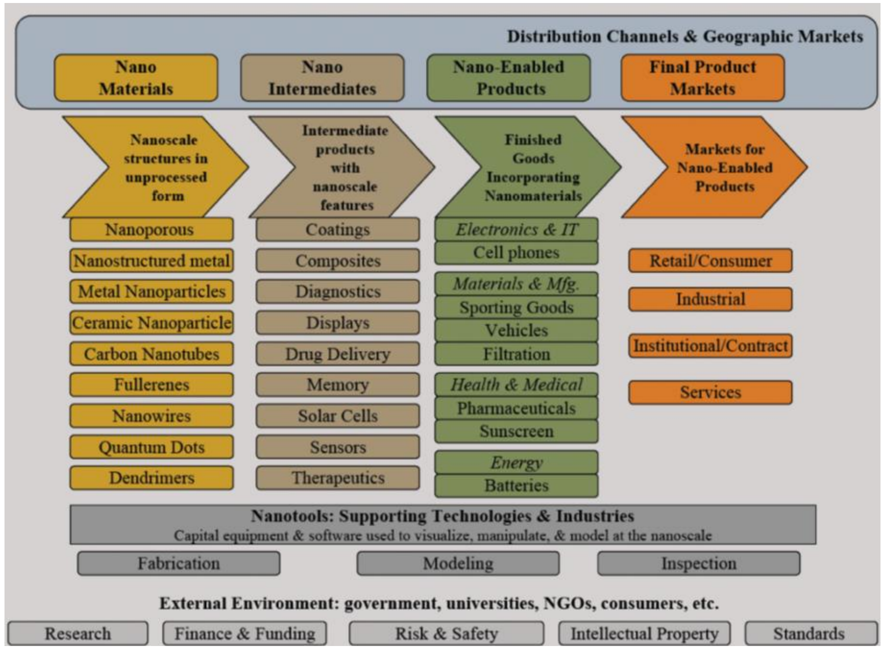


Figure 11. Value chain of nanotechnology from material to products (Ref. 23)

In terms of industrial classification of nanomaterials, the major share of the nanoscale materials account to nanostructured metals, metal nanoparticles, ceramic nanoparticle, carbon nanotubes, fullerenes, nanowires, quantum dots and dendrimers, nucleic acids, nanofibers, polymer and co-polymer nanomaterials, proteins and other nanocrystalline materials.[282-285] These nanostructured materials can be used for nanointermediate products or nano-enabled final market products ranging from garments, cosmetics to health, technology, pharmaceuticals, transportation and energy (see Figure 11). Moreover, the product based nanotechnology industries have also induced further industries in the field of nanomaterial modeling and characterization, storage and transportation.[282, 286] These additional industries also usages nanomaterials and nanotechnology further increasing the market potential of nanoscale materials. Hence the industrial nanomaterials that are commercially used and the economic potential of these commercial nanomaterials are two important topics that will be discussed further in this study.

4.3 Industrial nanomaterials

The nanomaterials used in industries can be classified based on their physical properties and application. In terms of physical properties these nanomaterials can be classified largely as i) inorganic non-metallic nanomaterials, ii) carbon based nanomaterials, iii) metallic nanomaterials and iv) organic, macromolecular or polymeric nanomaterials.[287-289] Among these inorganic non-metallic oxides like silicon oxide, titanium oxide, iron oxide, carbon based nanomaterials like carbon nanotubes (single wall and multiwall), metallic nanosilver and organic materials like dendrimers and polystyrene are among the highly produced and commercially used nanomaterials.[290, 291] Since these materials are different in terms of physical properties hence their growth industry also differs accordingly. Moreover, the growth process and the growth chemistry are also different for each of these materials class. For example, inorganic and metallic nanomaterials can be synthesized by various chemical and physical processes like sputtering, laser ablation, mechanical milling, sol-gel, chemical vapor deposition and spray pyrolysis wherese carbon based nanomaterials can be largely synthesized by chemical vapor deposition technique.[292, 293] Similarly, organic and polymeric nanomaterials are largely produced by dry, wet or combined chemical synthesis techniques .[294]

Similarly, based on the application areas of nanomaterials there are various industries that have either produced or used nanomaterials as intermediate products or finished products. The major industries that usages nanomaterials can be classified as follows:

4.3.1 Food

Food industry is one of the rapidly developing industries in terms of applying new technologies. The approval of various nanomaterials in food and food industry by the regulating bodies in different countries and adopting new technology developed from nanotechnology is thus expected to increase the market value of food based industry.[288] The main avenues in food industries using nanomaterial and nanotechnology are food processing, packing and delivery. In the area of food products, nanomaterials can improve the nutrient content as well as the bioactive delivery systems, texture and flavor encapsulation and microbiological control while the nanoparticles in food processing and packing are used either as antimicrobial or to build high sensitivity biosensors for detecting pathogens, allergens and contaminants.[295] The majority of the nanoparticles investigated and used either directly or incorporated indirectly in the food sectors are silicon dioxide, silver, titanium dioxide and zinc oxide.[272, 296, 297] Silicon dioxide nanoparticle, for example has been used as anticaking agent in the form of synthetic amorphous silica (SAS) and is also registered in European union (EU) as food additive. Furthermore, SAS is used as clarifying agent for beverages and anti-caking agent in many powered food items and health care products like toothpaste, detergents and cosmetics.[298]

Similarly, titanium di-oxide nanoparticles has been used in food industry as a pigment to enhance the white color of dairy products and candy, as an food addictive and flavor enhancer in dried vegetables, nuts, seeds, soups, mustard, beer and wines.[299] Titanium di-oxide nanoparticle is also used in some industries as antimicrobial agent by combining with other materials like nickel oxide and cobalt.[300]

Silver nanoparticles is one of the most investigated and used nanomaterial in food and biomedical industry. The strong biocidal, antimicrobial, antifungal activities of silver in nanomaterial form has thus been used to color the external coating of confectionary, decorate the chocolates and liqueurs.[301]

Similarly dietary supplement is another emerging market where titanium di-oxide and silicon dioxide are commonly used.[302]

Zinc oxide nanoparticles have been used as a food additive mainly as a zinc source in ceral-based foods. Due to its antimicrobial property, it is also incorporated into the linings of food cans for meat and food products mainly to preserve the color and to prevent the spoilage.[303, 304]

Iron and selenium nanoparticles are additional materials that has high prospective in food based products. Health issues related to micronutrient deficiency in human and animals can be supplied using nanomaterials and iron and selenium are one of such nanomaterials which can fulfill the iron deficiency as well as increase the selenium absorptivity in body.[305-307]

Similarly for the food preservation, nanoparticles embedded thermoplastic polymers or carbon nanotubes, metal, metal oxide nanoparticles as fillers in packing industry can enhance the quality and stability of foods.[308-310] Nanocomposite films enriched with silicate nanoparticles or carbon nanotubes is also used in plastics beer bottles to increase the material strength.[311, 312] The food packing industry also usages nanomaterials of silver, zinc oxide, titanium di-oxide because of the antimicrobial, biocompatibility and non-toxicity properties.[313, 314] Similarly, the composite of nanomaterials, nanoclay, nano-encapsulate and polymer nanomaterials derived from natural sources are additional nanomaterial bases resources that are intensively researched and commercialized for food processing, packing, food contact material or as a food supplement.[315] The overview of the nanomaterials in various food based industry is summarized in Figure 12.

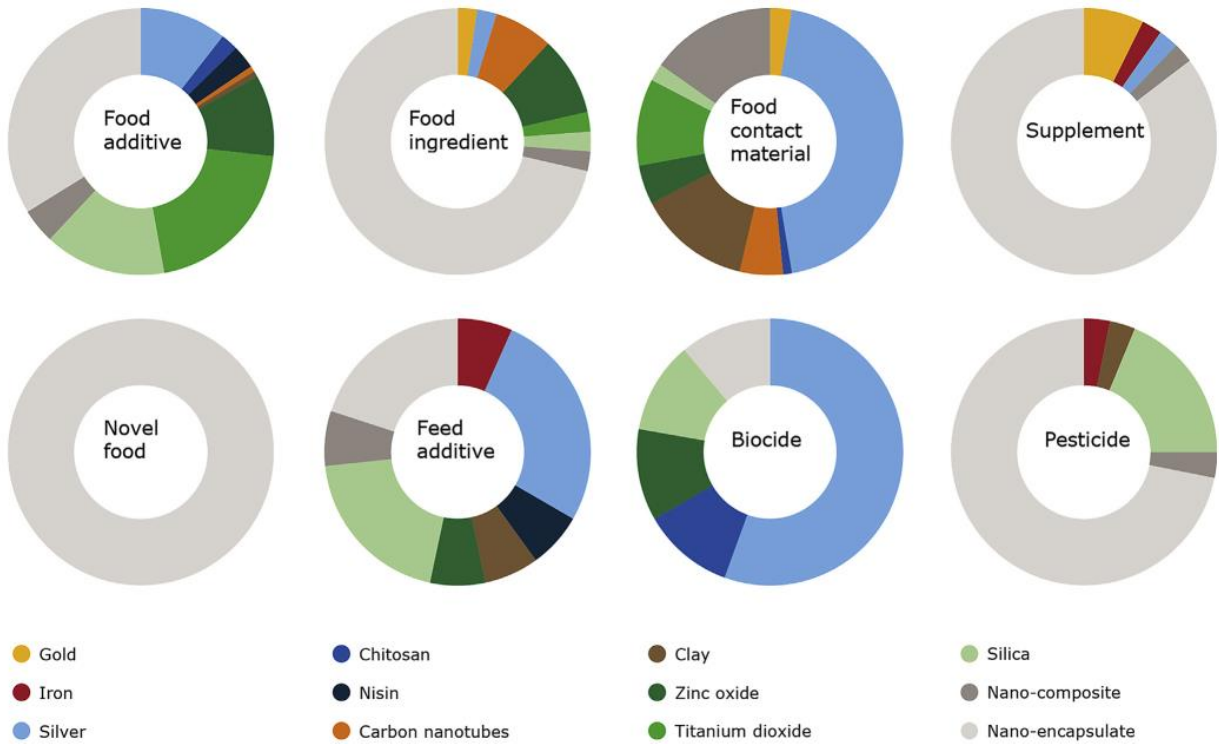


Figure 12. The most frequently used types of NM in applications in agri/feed/food. The listed types of NM represent about 75% of the identified applications. Exact numbers can be found in the original report (Ref. 53).

4.3.2 Agriculture

The various issues related to chemical fertilizers like the low chemical absorption in soil, soil toxicity from the fertilizers and harmful food production have induced new research in agriculture. These researches mainly focuses on organic agriculture with the use of organic pesticides, fungicides and technologies related to organic agriculture.[316] Moreover the current research trend is to use nanomaterials and nanocompounds and monitor the agriculture productivity and the physio-chemical state of soil using nanotechnology.[317, 318] For example, silver nanomaterial and carbon nanotubes are considered as an essential micronutrient source for the plant and these materials can also be used as organic pesticides, can play important role in plant protection and both these nanomaterial are important component of nanosensors to detect plant based pathogens and to monitor the plant and soil physical state.[319-322] Similarly, the essential micronutrient like copper, iron, manganese, molybdenum, zinc, cobalt can be synthesized in nanostructure form and they have thus been an essential component in the organic fertilizer and organic pesticide industries.[323, 324] Similarly, porous hollow silica is being used for the control release of the pesticides while nanosized carbon particles and metal nanoparticles have been studied for insecticides, antimicrobial and antifungal properties that can be used for plant protection.[325-328] Along with crop protection and pest control, nanomaterial can also boost the crop production along with increasing the quality of the crop which eventually reduces the quantity of fertilizer for crops.[329-332] Furthermore, the ability of soil and root to absorb the nanomaterials also increases the nutrient content in the food.[333]

4.3.3 Technology

The largest market share of the nanomaterial consumption accounts to the technology based industry. From optical devices to electronic, energy storage to production, sensors and bio-medical devices are the major avenues that are currently commercialized with the use of nanomaterials .[334] The use of organic and inorganic nanomaterials in modern devices is due to their unique physical and chemical properties like tunable electronic bandgap, large surface to volume ratio, high photoluminescent, faster electron transport, wide range of material choices and low material consumption.[335] For example, the modern light emitting devices (LED) usages semiconductor nanomaterials like indium gallium nitride, aluminum gallium indium phosphide, aluminum gallium arsenide and gallium phosphide.[336] However the low availability of these materials and the toxicity related issues has induced new research and development in the field of LED. Hence, quantum dots and polymers like cadmium selenide, zinc cadmium selenide, ruberene, tetracene, pentacene and other nanostructure materials like carbon nanotubes and 2-dimensional molybdenium di-sulphide, tungsten selenide and blackphosphorous are currently explored.[336, 337] Similarly, the miniaturization of transistor in electronics devices and the need of flexible and high luminescent optoelectronic device is expected to be replaced by nanostructure materials like carbon nanotubes, atomically thin germanium, tetracyanoquinodimethane, tetracene, monolayer of molybdenium di-sulphide/telluride, tungetein di-sulphide/selenide and black phosphorous.[338] Similarly, nanostructure silicon, carbon nanotubes, graphene oxide and polymer and co-polymers like polyaniline, polypyrrole, poly(benzobisimidazobenzophenanthroline) are either commercialized or currently being explored intensively for their use in lithium and sodium based rechargeable batteries and supercapicators.[339-342] Energy producing devices is another emerging field where nanostructure materials like thin film gallium arsenide, copper indium gallium sulphide, cadmium telluride, amorphous silicon; polymer light absorber like organic dyes, perovskites and quantum dots based solar cell using lead sulphide/selenide are commercialized.[343] Similarly, expensive and rare materials like platinum in oxygen reduction/hydrogen evolution reaction (ORR/HER) are currently being replaced by iron oxide, graphene oxide, quantum dots of lead sulphide/selenide and 2-dimensional materials like molybdenum di-sulphide .[344] Similarly, another rare material like titanium in aircrafts bodies are being replaced by composite of carbon nanotubes and aluminium .[345] Atomic imaging and nanostructure microscopy equipment at present are also employing nanomaterials of gold to enhance the optical contrast along with various other new technological tools like displays based quantum-light emitting diodes, smart windows and nanosensors.[273, 346]

4.3.4 Disease diagnostic and treatment

The current research trend in disease diagnostic and treatment is use high resolution imaging of human body and using targeted drug delivery system to treat the specific region of the infection. For this various organic nanoparticles have been widely investigated with liposomes, polymersomes, polymer constructs and micelles for both imaging and drug delivery.[347] These nanoparticles which have size range ranging from 100 to few nanometers can easily infuse into the cells or even permeate along the blood vessels into specific body parts.[273] More important magnetic nanoparticles like iron oxide have huge advantage in modern high resolution imaging and drug delivery as compared to conventional techniques. This is because iron can be guided through external magnet inside the human body and iron or iron oxide nanoparticles can be bind or functionalized with drugs for targeted delivery.[348] Similarly, for systems using light based imaging instead of magnetic, gold nanoparticles with their plasmonic properties offers excellent biological imaging.[349] Similarly, other nanoparticle like silver and copper also offers similar plasmonic resonance in the visible region as like gold nanoparticle .[350] Apart from imaging, these nanomaterials also offers molecular functionalization for targated drug delivery.[351] These metallic nanoparticles are also more stable and less susceptible to photobleacing as compared to organic dye molecules that are traditionally used in diagnostic and delivery. Similarly, carbon nanotubes and semiconductor nanoparticles like titanium oxide nanotubes are also extensively explored for targated drug delivery due to their optical bandgap and the large surface area for drug functionalization.[352, 353]

4.3.5 Cosmetics and daily consumable products

Many of the commercial nanomaterials like titanium di-oxide, silver, silicon di-oxide and nanoclays are one of the important ingredients in cosmetic products and daily consumable products. For example fumed silicon di-oxide nanoparticle of size between 5 and 100 nm is used as anti-caking agent in cosmetics and toothpaste and as an antifoaming agent in decaffeinated coffee and tea.[288, 354] Similarly, titanium di-oxide due to its large bandgap and as its strong oxidation potential is used in sunscreen for protecting against ultra-violet light and in toothpaste as whitening and cleaning agent.[288] Similarly many of the anti-aging products, hair care and coloring materials, shampoos, deodorants and shaving cream also contains titanium di-oxide or silver nanoparticles.[355] Zinc oxide is another large bandgap materials that is also used as bulking, skin protector, colorant and as an UV-filter similar to titanium di-oxide.[356] Nanoclay are another class of natural nanomaterials that are recently being used in various cosmetic products.[357-359] These nanomaterials are obtained from refined pure black soil, natural minerals, charcoal and natural plant pigments.[360]

4.4 Economic value of nanomaterial based products

The use of nanomaterials in food, technology based products, agriculture, cosmetic and biomedical products have increased the research and commercialization of traditional and new nanomaterials.[361] The economic value of these nanomaterials have also surged and more is being invested in finding cost-effective and multifunctional nanoscale materials. At present 6059 different nanomaterials based products are commercially produced in 47 different countries mainly in cosmetics, construction, textile and food (see Fig. 13).[362]

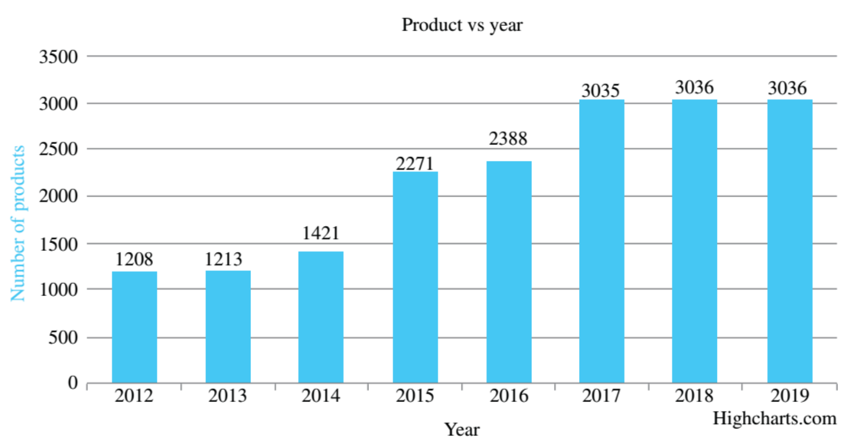


Figure 13. Number of products using nanomaterials in the period from 2012 to 2019 (Ref. 100)

Among these products silver and titanium di-oxide based nanomaterials and carbon nanotubes are the major component used in the commercial product (see Fig. 14).[363] More importantly, the global nanomaterial market is projected to reach more than 55 billion by 2022 with an annual growth rate of 20.7% in sectors like biomedicine, electronic, energy, environment and pharmaceutical (see Fig. 15).[364, 365]

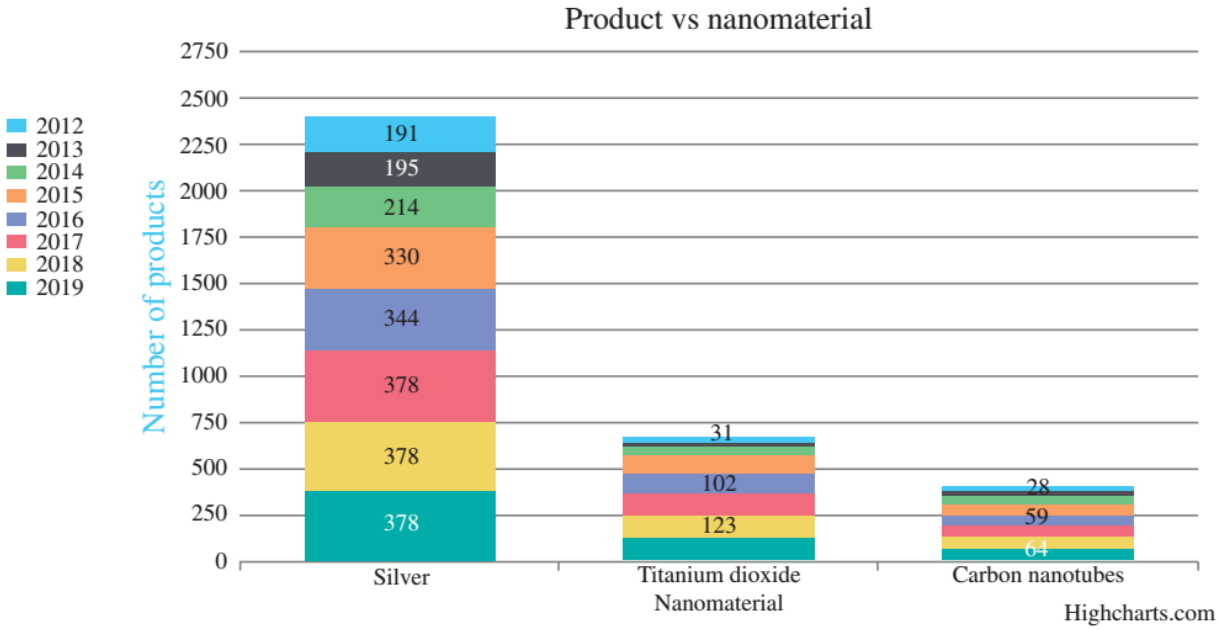


Figure 14. Number of products and type of nanomaterial in the period from 2012 to 2019 (Ref. 101)

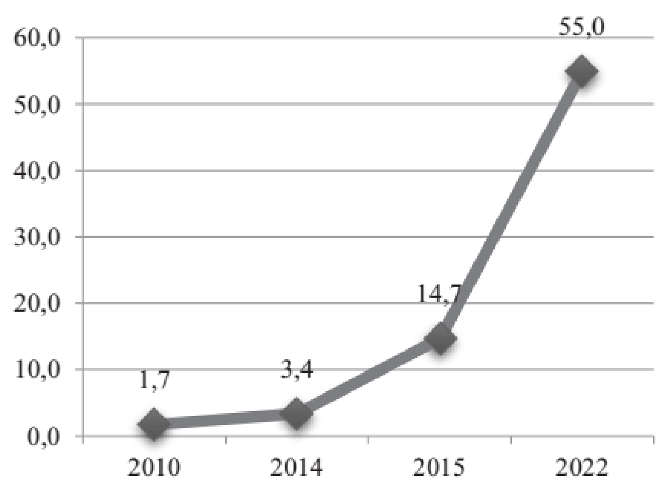


Figure 15. Global value of nanomaterials, optimistic view (USD billion) (Ref. 103)

In terms of nanomaterials, silver nanoparticle solely accounts over 50% of the market share and this value is expected to increase at a rate of 13% till 2024.[366] The main industrial consumption of silver nanomaterial is in healthcare, life sciences, food , beverage packing, electronic and IT secotrs. Similarly nanoclays, nanocomposite materials and quantum dots are other important nanomaterials which are being consumed and have large industrial potential (see Fig. 16).[365, 367, 368] Similarly, the industries like aerospace, sporting goods, automotive, energy storage, electronics and defence are emerging economic sectors which will heavily rely on the nanomaterial and nanotechnology.[369]

Selected nanomaterials market	Global market revenue by 2016, USD billion	Expected global market revenue by 2021, USD billion	Expected CAGR in 2016-2021, percent
Silver nanoparticles	1.1	3.0	13
Nanoclays	0,7	2,1	24,9
Nanocomposites	1.6	5.3	26.7
Quantum dots	0.61	3.4	41.3
Nanofibers	0.39	2.0	38.6
Advanced & nanoscale ceramic powders	14.6	22.3	8.9

Figure 16. Nanomaterial market size for selected nanomaterials (CAGR: compound annual growth rate). (Ref. 103-107)

4.5 Nepal's status in nanomaterial and nano-compound market

Nepal's economic market is mostly import dependent and except few garment, essential oils, flavored species, lentils and timer products, Nepal merely exports any substantial product that have an impact in national economy. However, the large natural resource can be one potential source to initiate nanomaterial and nano-compounds based product that have demands in global market. One of these industrial market using natural resource can be pharmaceutical products, mostly raw materials for medicine and food products. Since 2013, Nepal import in medicinal and pharmaceutical products have been rising and have reached a market value of USD 47,503,000 in

2019 (see Fig. 17).[370] Nepal mainly imports 11433 types of pharmaceutical raw materials and assorted pharmaceutical products from India, China and other countries which are later processed in consumable products in Nepal.[371] However from 2013 onwards, Nepal have also initiated exporting medicinal products mainly in India, Sri Lanka and Bhutan.[372] These pharmaceuticals exports was estimated to be around USD 4.94 million in 2017 (see Fig. 18).[373] Besides this, Nepal also exports traditionally grown spices like ginger, cardamom, turmeric, cinnamon and chillies to India, Pakistan, Singapore, Germany and Taiwan.[374] These exports mainly accounts to raw powder products rather than finished products. Similarly few organic chemicals like Sulphonamides and heterocyclic compounds and essential oils and resinoids (perfumery, cosmetic materials) are some of the raw products that have being exported from Nepal.[374] Moreover, the high value medicinal and aromatic plants (MAP) and slowly being industrialized to develop products for national and international markets. It is estimated that export of MAP products increased from USD 27.49 million in 2005 to USD 60.09 million in 2014 with an average annual export of 13.23 thousands ton in 50 different countries (see Fig. 19).[375]

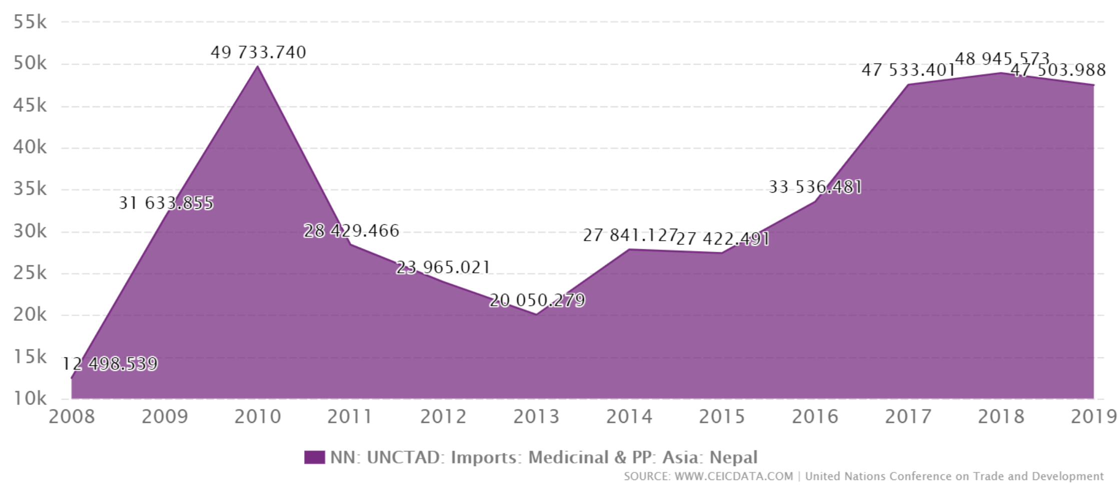


Figure 17. Medicinal and pharmaceutical product import value in Nepal (value in thousand USD)

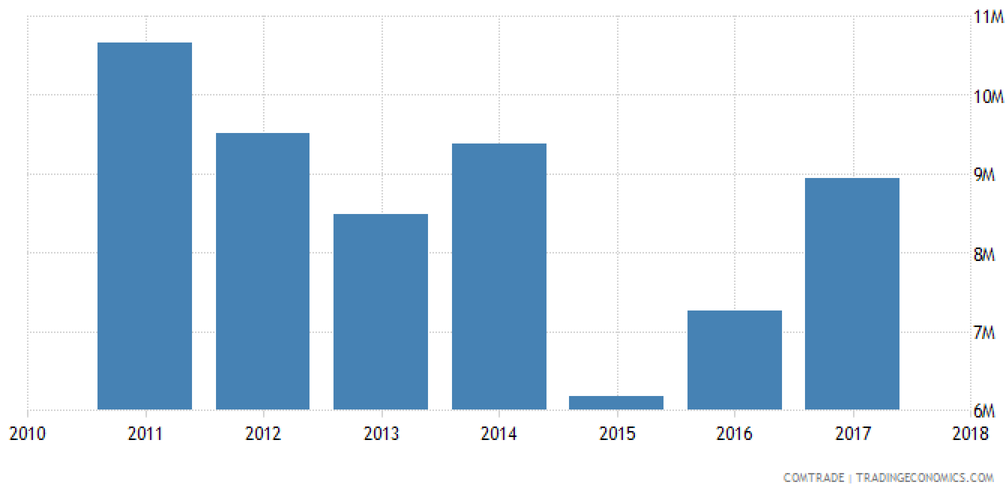


Figure 18. Nepal's export of pharmaceutical products

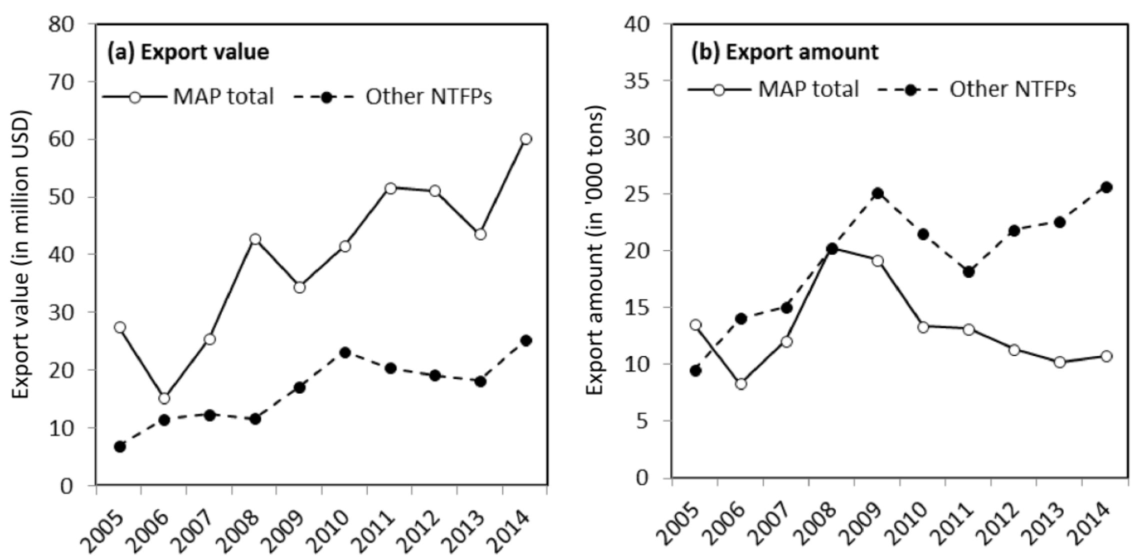


Figure 19. Trend of MAP and other non-timber forest product (NTFP) export from Nepal between 2005-2014

4.6 Prospective

The race to find smart, efficient and miniaturized devices, healthy and nutritious food and environmentally compatible technology has brought a global economic opportunities in the field of material research and commercialization. The current focus in the world nanomaterial market is to increase the market penetration of existing materials, decrease the price of nanomaterials and products, improve materials and product properties, expending research and development activities related to new materials, increase private and public financing in nanotechnology research and initiate co-operation between countries for research and product development. Moreover, only few of the nanomaterials are currently produced commercially and there are many important issues within the research and industrial community that has restricted the commercialization of the nanomaterials and its products. Some of these issues are related to the stability, toxicity, large scale growth of nanomaterials and its integration in devices and technologies. These issues have restricted the large scale economic potential of nanomaterial and nanotechnology but on the other hand these material issues have also induced new research and industrialization scopes. For example, the issue related to chemically synthesized materials is slowly being replaced by green synthesis techniques using natural products and natural resources. The green nanomaterial is also viewed as the next nanotechnology product especially in the field of biomedical and drug discovery. Hence the market opportunities of nanomaterial growth and optimization in terms of stability and toxicity as well as the product related to green nanotechnology are slowly emerging. Hence countries like Nepal which have rich diversity in plants, crops and flower species have better opportunities in penetrating this emerging market. For example, 6391 flowering plant species, 161 species of high altitude medicinal plants that can be used in medicine, essential oil, dyes, species and constructions have been identified. Besides these, the large amount of agricultural crops and forest waste can be utilized for various commercial industries like fertilizer development for agriculture industries, nanomaterial synthesis for various new emerging technology based industries based on organic semiconductor synthesis, solar cell, batteries, light emitting diodes and for polymer synthesis for application in automobiles and steel industries. Considering the huge economic potential of the nanomaterial, it is expected to be a common technology for large industries and due to the global economic benefit more than 60 countries have launched nanotechnology development strategies in their national agenda for science and technology development. Hence Nepal should also consider utilizing the huge national resource of medicinal plants and forest and agriculture products in developing nano-technological products and industries in order to gain economic benefit from these resources.

Chapter 5. Nanotechnology based high gain and efficient procedure for natural product extraction

5.1 Natural product extraction methods

Phytochemicals are the essential component of natural product extract derived from plant and flower species.[376] There are various chemicals and compounds present in various plant species (see Fig. 6) which can be effectively extracted for various applications ranging from medicines, food, additives, food supplements, technology and agriculture.[376] These phytochemicals can be obtained using various traditional and modern methods. Compared to conventional techniques which are lab-intensive and time consuming, the modern extraction techniques are developed to increase the yield and enhance efficiency. However the extraction process itself cannot provide the required natural product extract. Dissolving of the solutes in the solvent, diffusion of the solute out of solid matrix, separation of the solute and collection of the solute extracts are other important process to obtain high yield desired natural products (see Fig. 20).

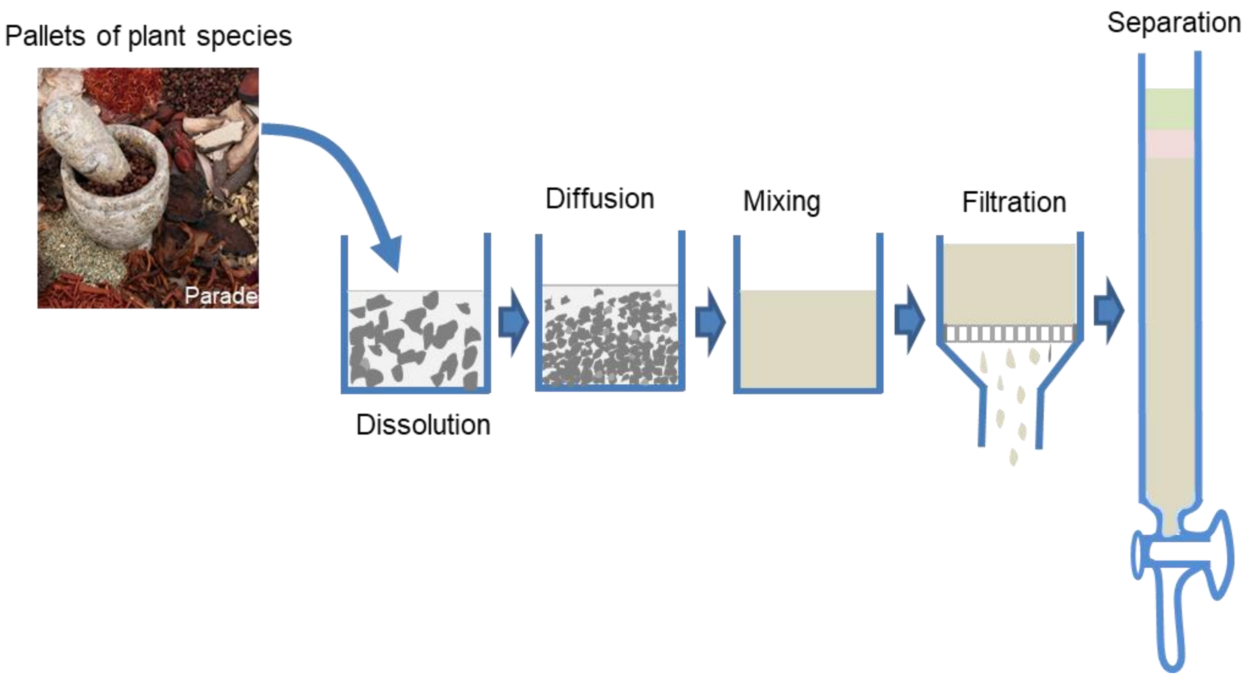


Figure 20. Various process involved in the natural product extraction

The various traditional and modern methods used in the natural product extraction are presented below:

5.1.1 Maceration

This is one of the most simple extraction techniques which usages the raw material from natural sources to contact with the solvent for a particular period with frequent agitation for natural product extraction.[377] Maceration is a traditional technique where the active ingredients from the natural sources cannot be completely extracted. Hence this technique is mostly used for the extraction of thermolabile components only.[377, 378]

5.1.2 Percolation

In percolation, the raw materials are moistened with the solvent and placed in a narrow cone shaped chamber. Percolation follows the similar principal as like maceration. However percolation as compared to maceration is a continuous technique where the solvent used in product extraction are constantly replaced by fresh solvent.[377, 379]

5.1.3 Decoction

Decotation usages boiling of the raw materials to obtain product extract. Hence the extract from decotion contains large amount of water soluble impurities. [378] This method cannot be used for extraction of thermolabile or volatile components.

5.1.4 Soxhlet extraction

Soxhlet extraction is used when the desired extract has a limited solubility in specific solvent. This technique utilizes reflux and siphoning to continuously extract the herb with fresh solvent. [380] It is a continuous process with high extraction efficiency and requires less time and low solvent consumption.

5.1.5 Supercritical fluid extraction (SFE)

SFE usages supercritical fluid like supercritical carbon dioxide, nitrogen, methane ethane, ethylene, nitrous oxide, sulfur dioxide, propane, propylene, ammonia and sulfur hexafluoride as the extracting solvent. [381, 382] The raw materials for extraction are filled with the gas under controlled conditions of temperature and pressure. Supercritical fluid has similar solubility to liquid and similar diffusivity to gas. Hence it can dissolve wide variety of natural products.

5.1.6 Microwave assisted extraction

In this method microwave energy are used as an external agent to separate active ingredients from raw material into the solvent for extraction. The electric field in microwave generates heat by dipolar rotation which in turn disrupts bonds of the solvent to penetrate into the sample matrix. [383, 384] Microwave extraction can thus accelerate the extraction process to increase the extract yield, transfer heat selectively into the solvent and decrease the thermal degradation process. This technique can also be used for solvent free extraction, usually for volatile compounds and thus can also be considered green extraction technique.

5.1.7 Pulsed electric field (PFE) extraction

PFE extraction is a non-thermal method which decreases the degradation of thermolabile compounds and thus increases the extraction yield and decreases the extraction time. [378] The electric field used in the extraction process can increase mass transfer during extraction by destroying membrane structure of the solvent and raw material.

5.1.8 Ultrasound assisted extraction (UAE)

This advanced technique as compared to other usages acoustical cavitation to disrupt the cell wall of the raw materials so that the solvents can penetrate easily. [385] UAE has the ability to extract large amount of bioactive compounds within short extraction time. Since this technique uses low temperature, hence the thermally unstable compounds can also be extracted easily.

5.1.9 Accelerated solvent extraction

In ASE, solvent are used at elevated temperature and pressure so that the solvent are in liquid form in order to increase the solubility and diffusion rate of the solvent into the matrix of raw materials. [386] The pressurized solvent further increases the diffusion and penetration depth of the solvent. This method usage very low quantity of the solvent and also reduces the reaction time.

5.1.10 Enzyme assisted extraction (EAE)

EAE usages hydrolytic action of the enzymes like cellulose, α-amylase and pectinase on the components of the cell wall and membrane and the macromolecules inside the cell which facilitate the release of the natural products.[387]

5.1.11 Hydro distillation and steam distillation

This is a commonly used method for the extraction of volatile oil. Hydro distillation is a conventional technique where the raw materials for extraction are boiled in water and this technique was improved using steam distillation in which steam is passed through the raw materials to extract the natural compounds.[388]

5.1.12 Cavitation technology based extraction

This techniques usages the idea of forming bubbles to create a pressure and temperature variant inside the extraction system. Cavitation phenomenon can be created by different techniques like hydrodynamic force, heat, electric discharge and high pressure steam injection.[389] This is also considered as one of the green technology based extraction techniques which have high implementation in industrial scale.

These various methods for extracting natural product can be summarized as:

Method	Solvent	Temperature	Pressure	Time	Volume of organic solvent consumed	Polarity of natural products extracted
Maceration	Water, aqueous and non-aqueous solvents	Room temperature	Atmospheric	Long	Large	Dependent on extracting solvent
Percolation	Water, aqueous and non-aqueous solvents	Room temperature, occasionally under heat	Atmospheric	Long	Large	Dependent on extracting solvent
Decoction	Water	Under heat	Atmospheric	Moderate	None	Polar compounds
Reflux extraction	Aqueous and non-aqueous solvents	Under heat	Atmospheric	Moderate	Moderate	Dependent on extracting solvent
Soxhlet extraction	Organic solvents	Under heat	Atmospheric	Long	Moderate	Dependent on extracting solvent
Pressurized liquid extraction	Water, aqueous and non-aqueous solvents	Under heat	High	Short	Small	Dependent on extracting solvent
Supercritical fluid extraction	Supercritical fluid (usually S-CO_2), sometimes with modifier	Near room temperature	High	Short	None or small	Nonpolar to moderate polar compounds
Ultrasound assisted extraction	Water, aqueous and non-aqueous solvents	Room temperature, or under heat	Atmospheric	Short	Moderate	Dependent on extracting solvent
Microwave assisted extraction	Water, aqueous and non-aqueous solvents	Room temperature	Atmospheric	Short	None or moderate	Dependent on extracting solvent
Pulsed electric field extraction	Water, aqueous and non-aqueous solvents	Room temperature, or under heat	Atmospheric	Short	Moderate	Dependent on extracting solvent
Enzyme assisted extraction	Water, aqueous and non-aqueous solvents	Room temperature, or heated after enzyme treatment	Atmospheric	Moderate	Moderate	Dependent on extracting solvent
Hydro distillation and steam distillation	Water	Under heat	Atmospheric	Long	None	Essential oil (usually non-polar)

Figure 21. Brief summary of various extraction methods for natural products (Adopted from Ref. 11)

5.2 Natural product separation methods

The various techniques described above and summarized in Table 1. produces natural product extract in crude form. Hence separating the components from the extract to obtained the desired biological compounds and further purification of these compounds to use them in research and commercial products are additional component of natural product extraction. The separation of the biological compounds from the crude extract depends on the physical and chemical properties of the natural compounds and column chromatography is the main method used for obtaining pure natural products. Hence, there are various chromatography techniques based on the physical and chemical properties of extract which are commercially used for separating biological compounds in the natural extract. These are explained below:

5.2.1 Separation based on adsorption properties

This separation technique is based on the difference between the adsorption affinities of the natural products.[390, 391] For this adsorption column chromatography is widely used for the separation of natural products especially in the initial separation stage. This is a simple, high capacity and low cost technique which usages silica gel and macroporous resins as the adsorbents. Silica gel is a polar absorbent which have silanol functional group and thus the functional group can retain the compounds in the extract.[392, 393] This is the most widely used absorbent in phytochemical separation in preparative scale. Similarly, adsorptive macroporous resins are polymers with macroporous structures which can selectively adsorb many natural products.[394-396] They can be used as a part of the pretreatment process of natural products and at times can also be used for the complete separation of natural compounds from the raw extract. The various factors for adsorption in macroporous resin induces electrostatic forces, hydrogen bonding, complex formation and size-sieving action between resins and natural products in solution.

5.2.2 Separation based on partition coefficient

This method is based on the relative solubility in two different immiscible liquids.[397, 398] For this partition chromatography is used which follows the liquid-liquid extraction principle based on the relative solubility. Silica gel, carbon or cellulose are used in the early stage of separation as one stationary liquid phase and other liquid as a mobile phase for the effective separation of raw extract using partition chromatography.[399]

5.2.3 Separation based on molecular size

In this method two different techniques, membrane filtration and gel filtration chromatography are employed for the separation of natural product extract. In membrane filtration, the semipermeable membrane allows smaller molecules depending on the size of the membrane to pass through while restricting the larger molecules.[400, 401] Depending on the pore size of the membrane various filtration can be applied like microfiltration, ultrafiltration and nanofiltration.[401, 402] Depending on the purity level and the physical state of the extract, coupling membrane filtration can also be applied which usages combination of multiple membrane filters.

Gel filtration chromatography is a size exclusion chromatography technique which usages gel permeation technique to separate the component of the extract.[403, 404] The separation in this chromatography is dependent on the retention time which is larger for smaller molecules as compared to larger molecules in the matrix of natural extract.

5.2.4 Separation based on ionic strength:

This technique uses ion-exchange chromatography to separate molecules based on the difference in their net surface charge.[405, 406] The charged molecules in the natural extract could be caught and released by ion-exchange resin by changing the ionic strength of the mobile phase by either changing the pH or salt concentration. Here the cation ion-exchange resins are used for the separation of alkaloids while the anion ion-exchange resins are used for the separation of natural organic acids and phenols.

5.2.5 Molecular distillation:

Molecular distillation is used for separating thermosensitive and high molecular weight compounds. It can separate the molecular components in a natural extract by distillation under vacuum at much lower temperature compared to its boiling point.[407]

5.2.6 Supercritical fluid chromatography:

This technique usages supercritical fluid for separation of natural compounds from raw extract.[408] The supercritical fluid possess properties of high dissolving capability, high diffusivity and low viscosity allowing rapid and efficient separation of non-volatile or thermally labile compounds.

5.2.7 Simulated moving bed chromatography:

Simulated moving bed chromatography uses multiple columns with stationary phase.[409, 410] The counter current movement of the bed is simulated through rotary valves which periodically switch the inlet for feed and outlet for the extract. This is thus a continuous separation method and can be used for large scale separation of natural products with low solvent consumption and more importantly at a very short reaction time.

5.2.8 Multi-dimensional chromatographic separation:

Multi-dimensional separation is based in the solid phase extraction coupled to multiple columns with different stationary phases.[411] This can thus improve the compound separation efficiency in a raw extract which is complex and hard to extract by single phase separation techniques.[412, 413] Also the multi-dimensional separation can be achieved using the same equipment as compared to other techniques which usages pre-separation and purification.

5.3 Natural product extraction/separation using nanotechnology and other advanced techniques

Current requirement in natural product extraction is to enhance extraction speed and produce high gain and efficient natural product extracts. For this various stand alone and combined extraction and filtration techniques using pressure, voltage and temperature are designed and being implemented. At present, the use of nanotechnology based extraction techniques are extensively being researched as they can enhance extraction speed and provide high purity chemicals and compounds. Some of these techniques that can be used conveniently for laboratory and industrial application are described below:

5.3.1 Solvent free extraction

Solvent free extraction mainly usages external medium like temperature and current to decompose a raw material that can later be used for extraction of essential components in a natural product extract.[414] This external medium for decomposition is supplied through various technological means like pulsed electric field, laser and microwave sources. The two main techniques used in solvent free extraction as explained below are:

i) Microwave assisted extraction and

ii) Pulsed electric field extraction

However, the effectiveness of both these system depends on parameters like field strength, specific energy input, treatment temperature and output yield. In terms of microwave assisted extraction, vacuum and temperature can be added as additional mediums so as to enhance the raw material decomposition rate and collection of essential phytochemical components in the material.[415, 416] Introduction of vacuum into the microwave chamber for extraction can enhance the decomposition rate as the ion penetration depth can be enhanced as well as the crude extract can be effectively collected under vacuum condition without further need of distillation and evaporation.[417] Some of the example of this technique has been applied in the extraction of essential oil from mint (Mentha spicata L., Mentha pulegium L.).[418] Similarly, temperature of the system can play another important role in the phytochemical extraction and introduction of external temperature within the microwave chamber can enhance the rate of raw material decomposition as well as increase the reactivity of ions within the material.[419] This can be achieved by introduction of laser or ultra-violet light based heating within the microwave chamber so that both dipole generated heat from microwaves and laser assisted heat can simultaneously decompose the raw material as well as the phytochemical components of the crude extract.[414, 420] The temperature dependent microwave extraction can also eliminate the need of evaporating the crude extract for extracting desired compounds in the natural extract.

Similarly, pulsed electric field using short duration pulses of moderate to high electric fields (0.1-50 kV/cm) can cause temporary to permanent rapturing of membrane structure of the plant species.[414] However the high energy requirement in electric field based extraction can be compensated by coupling external medium like pressure and temperature into the extraction chamber as described before in microwave assisted extraction process. The pressure and temperature can play a key role in reducing the high electric field requirement, enhance the decomposition rate of extract and eliminate the need of distillation and evaporation. These combinational approaches in extracting high yield and efficient techniques are presented in Figure 22.

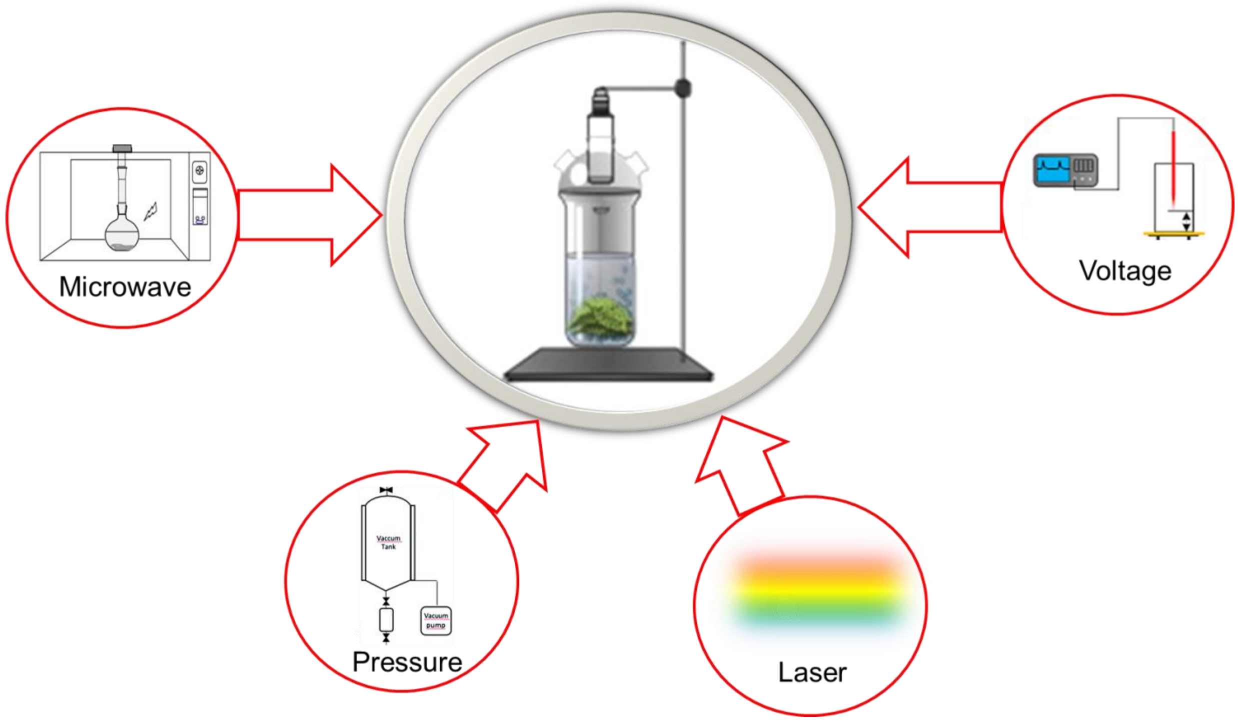


Figure 22. Choices in using various extraction techniques along with external mediums that can minimize extraction cost and enhance the efficiency and yield.

The overall advantage of using the solvent free extraction techniques are:

- Reduces extraction time and degradation of raw materials
- Direct extraction of plant cells to release metabolities
- Larger penetration depth for increasing the product yield
- Eliminates the need of additional components required for evaporation and distillation
- Economic as compared to energy required and solvent consumption in conventional techniques
- Easy upgrading from lab scale to industrial scale production

The presence of solvent and additional process required to purify the product from the solvent-mixed extract in conventional techniques can be greatly reduced in solvent free extraction. This thus makes this novel technique environment friendly with different selectivity to economic conditions and is thus considered green economic extraction technique.

5.3.2 Cavitation technology based extraction

Cavitation phenomenon generates transient bubbles and their collapse can generate several physical phenomenon like turbulence, shear forces, shock waves and microjets (see Fig. 23).[389] This physical phenomenon can be created by different techniques like hydrodynamic, laser, accelerated particles, electric discharge or steam injection.[421] Currently there are various cavitation based technologies like ultrasound assisted, microwave assisted, hydrodynamic and negative pressure based cavitation that are used for natural product extraction.[389] Introduction of ultrasonic waves of certain frequency, constriction in liquid flow or negative pressure in a system can create bubbles and pressure different which can be utilized to create high temperature or high pressure. This pressure or temperature can thus act as a medium to disrupt raw material, create highly reactive free radicals, enhance the mass transfer rate between solvent and substrate, increase surface area of matrix following disintegration and also increase the diffusion of solvents into substrates which can eventually increase the production yield and thus ease the natural product extraction phenomenon.[422, 423] The cavitation based technologies are thus gaining attention as greener extraction methods and are thus highly sought in pharmaceutical, nutraceutical and cosmetic manufacturing industries using natural resource as the source material.[424]

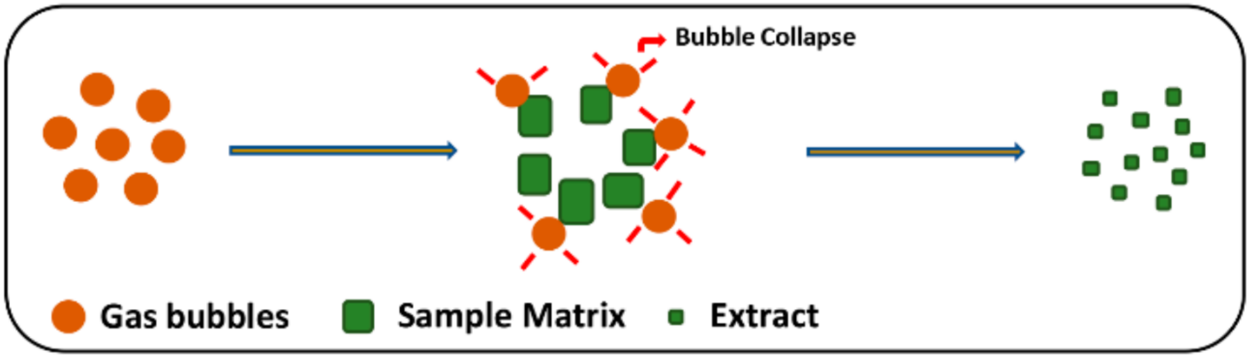


Figure 23. Overall mechanism of cavitation phenomenon (Adopted from Ref. 22)

The most commonly used cavitation extraction are based on hydrodynamic and negative pressure which has been applied in phytochemicals extraction producing with high yield. Some of the example includes lipid extraction from Microalgae Nannochloroposis sp. with a yield of 93% and protein from soyabean with 82% using hydrodynamic, flavonoids from Equisetum palustre L. with 57-89% using negative pressure.[425-427] However, the complexity of the system in creating hydrodynamic and negative pressure makes these process expensive than other conventional techniques. Hence the use of convenient techniques to create the cavitation or the combination of cavitation technology with other conventional techniques are some alternatives. Among these, cavitation with microwave assisted extraction and enzyme assisted technologies are currently being explored as a cost effective cavitation technology.

i) Cavitation and Microwave assisted extraction

In this technique the cavitation is created by ultrasound US) wave and the microwave (MW) are additionally employed to enhance the extraction yield and for the purpose of energy saving. The combination of US and MW can produce intense agitation which can rapture the matrix surface for efficient extraction. This combined technique can be operated together or sequentially depending the state of raw material and the natural compound to be extracted. Some example of the combined technique are presented below.

Raw material	Extract	Conditions	Yield	Reference
Pomelo peels	Pectin	MW: 643.44 W/6.4 min US: 40 kHz/27.52 min sonication	38%	[428]
Lotus seeds	Oligosaccharides	MW: 250 W US: 25 kHz/300 W	11%	[429]
Rhubarb	Anthraquinones	MW: 500 W US: 300 W	28mg/g	[430]

Table 8: Biological extraction using the combination of cavitation and microwave based techniques

ii) Cavitation and enzyme assisted extraction

Enzyme assisted extraction is known to degrade the impenetrable surface and cell walls but this technique along is time consuming. Hence the combination of cavitation with enzyme assisted extraction can reduce the extraction time and additionally enhance the yield since the enzyme can penetrate the larger surface regions created by the cavitation technique. In this combined technique, the convenient medium to create cavitation is by ultrasound wave which is economic and effective. Some examples of this combined technique are presented below.

Raw material	Extract	Conditions	Yield	Reference
Pumpkin	Polysaccharides	US: 34 kHz/440 W/51.5 ^{0}C Solvent water	4.33%	[431]
Mulberry must	Phytochemical: Total phenolics, Total flavonoids, Total anthocyanins	US: 34 kHz/60 W/20 ^{0}C Enzyme concentration: 0.01%	298.06; 379.24; 55.14 (mg/100 mL	[432]
Sisal waste	Pectin	US: 20 kHz/60 W Enzyme loading: 88 U/g at 50 ^{0}C	28 mg/g	[433]

Pomegranate seeds	Oil	US: 20 kHz/130 W/55 ^{0}C Enzyme loading: 2% w/w	95.8%	[434]

Table 9: Biological extraction using the combination of cavitation and enzyme based techniques

5.3.3 Membrane techniques for purification

The common purification techniques employed in conventional techniques like high pressure, concentration gradients and chemical and electrical potential difference works specifically for particular physical and chemical state of the extract. Moreover these conventional techniques come with sophisticated system which might increase the economic cost of industrial natural products. Hence membrane filtrations based separations are one of such convenient technique which can separate components of extract based on size of the components in the extract. Membrane filtration technique has been used as an industrial processing tool since early 1990s due to high product efficiency, simplicity, convenient operation and low energy consumption.[435] There are various types of membrane filtration based on the size of biological compounds and materials like microfiltration, ultrafiltration, nanofiltration, reverse osmosis, dialysis, electrodialysis, pervaporation, gas permeation and membrane distillation.[436-439] These techniques have a wide range of materials purification ranging from micromolecules to nanomaterials. For example reverse osmosis can be applied for molecules in the range of 0.1-1 nm while nanofiltration, ultrafiltration and microfiltration are used for molecules and macromolecules with molecular masses and molecular size ranging from 100-10000 ng and 10-1000 nm.[435] More importantly, the use of ultrafiltration and nanofiltration can provide an alternative to chromatography for the concentration and separation of desired natural products.[440] Some of the examples of various membrane filtration based purification techniques are presented in Figure 24.

Solute	Raw material	Membrane technique	Membrane material	Module	Surface area (m^2)	Pore size (μm)	Flux[b] (L/m^2h)
Phenolics	Almond skins	Centrifugal ultrafiltration	n/a	n/a	n/a	10–50k[a]	n/a
R-phycoerythrin	Macro-algae *Grateloupia turuturu*	Ultrafiltration	PES	Tubular	0.033	25–30k[a]	35.1
Pectin	Mature citrus peel	Crossflow microfiltration	Cellulose	Flat sheet	0.1	0.2	25.9
Galacto-oligosaccharide	Commercial mixture	Nanofiltration	Cellulose	Flat sheet	n/a	n/a	n/a
Fructo-oligosaccharides	Commercial mixture	Nanofiltration	n/a	n/a	1.77	n/a	n/a
Xylo-oligosaccharides	Rice husk xylan	Ultrafiltration	PES	Tubular	n/a	4k[a]	21
		Nanofiltration	Ceramic	Tubular	n/a	1k[a]	34
Xylo-oligosaccharides	Almond shells	Ultrafiltration	Polymeric	Flat sheet	1.26×10^{-3}	8k[a]	227–579
Xylose	Hemicellulose hydrolyzate feeds	Nanofiltration	PS	Flat sheet	0.18	150–300[a]	18.2–66.2
Hyaluronic acid	*S. zooepidemicus* fermentation broth	Tangential flow microfiltration and ultrafiltration	PVDF	Flat sheet	10.4×10^{-4}	100–300k[a]	23.0–24.9

PES polyethersulfone, *PS* polysulfone, *PVDF* polyvinylidene fluoride

[a] Molecular weight cut off, MWCO

[b] Dependent on specific pressure in each work

Figure 24. Application of membrane technique for primary purification of natural products (Adopted from Ref. 68)

Apart from single membrane filtration technique, combination of two or more membrane can be used for effective separation of wide range of natural product extracts.[441, 442] These combined purification techniques are employed sequentially and the first membrane can be used to separate solvents while successive membrane can filter natural products based on their molecular weight and molecular size. Some of the example includes combination of ultrafiltration and nanofiltration to purify benzylpenicillin from fermentation broth of Penicillium chrysogenum with a recovery yield of nearly 90%.[443] More recently, the use of nanomaterials like carbon nanotubes and 2D materials are viewed as next generation membrane materials for effective separation of nanosize molecules and nanomaterials from the raw extract.[444-447]

5.4 Scheme for natural product extraction

As explained in the previous section, specific choice of natural production extraction and separation technique depends on the physical state of the raw material, the quality of natural product extract, extract yield, cost of analysis, time for extraction and the physical state of the extract. The chart below summarizes the choice of technique used for extraction and separation of natural product and the extract.

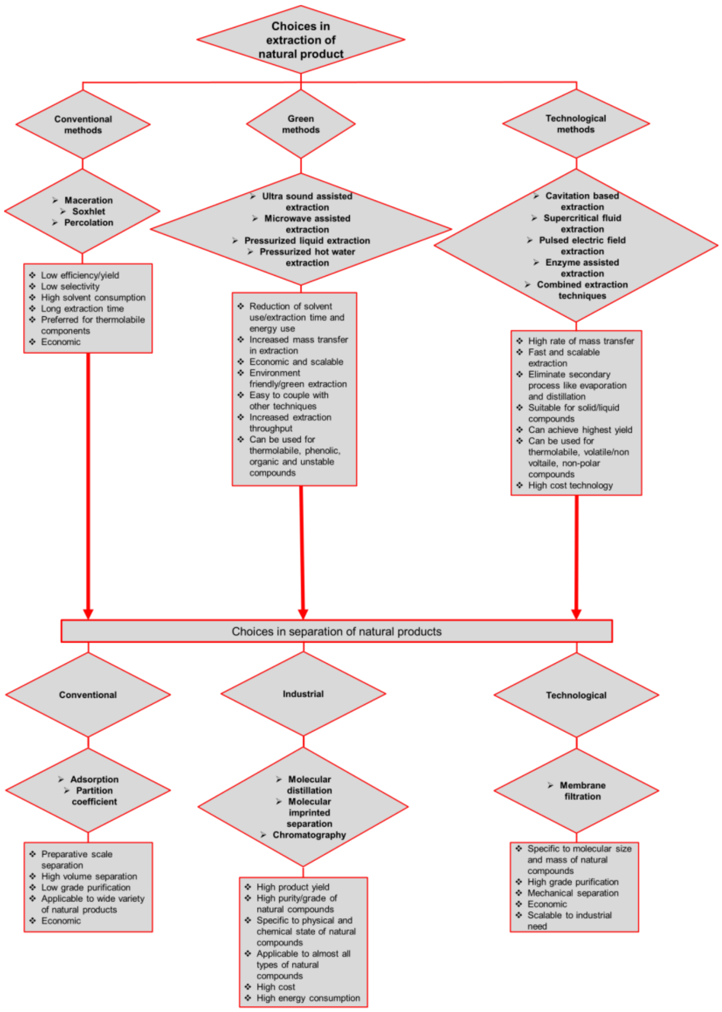


Figure 25. Various choices for natural product extraction

The basis of selecting the technique mainly depends on cost and the quality of the product to be extracted. The conventional techniques are cheap but the low grade purification of products in this technique produces low grade phytochemicals. To enhance the quality of product in conventional technique, various new technological components have to be introduced. However, the use of chemicals in these techniques can compromise the product quality. In order to enhance the quality of the product and the reliability of the technique, the green synthesis method is more preferred. Since most of the techniques used in the green synthesis method is physical process like ultrasound, microwave, pressure and temperature based synthesis hence this techniques guarantee product quality and reliability. However the large cost in using various techniques makes this process more expensive than conventional methods. Also, many of the volatile phytochemicals in plants needs additional technological resources to be added to the green synthesis method in order to compensate the issues of product volatility, low yield, low stability, etc. Apart from the conventional and green synthesis methods, the technological methods are high cost techniques that can be used for most of the phytochemical extraction. Due to various components in technological extraction like cavitation, supercritical fluid, electric field and enzymes add us the synthesis cost and time. Moreover, the components in technology extraction can be used as an additive feature in conventional and green extraction methods to enhance the quality of the product and the product yield.

Chapter 6. Non-toxic and sustainable nano-compounds and nanomaterials synthesis for electrical, optical and agricultural application

6.1 Introduction

Out of many nano-compound and nanomaterial synthesis procedure using physical and chemical methods, physical vapor deposition, chemical vapor deposition, sol-gel and colloidal methods are currently commercialized for large scale synthesis (see Figure 4).[187] Moreover, the high cost required in the material synthesis, toxicity of the material and the procedure along with the environmental issues arising due to toxicity have led to biological synthesis method using green chemistry approach .[188] Hence in our scheme of nano-compound and nanomaterial synthesis, we adopt the green synthesis procedure. This is mainly because biological synthesis method usages plant and microbes and these are present in large quantity in various geographical regions of Nepal, mainly from forest, agriculture products, flowering plants and wild and edible mushroom species.

6.2 Biological synthesis of nano-compound

The plant based biological compounds can be conveniently extracted using a simple extraction technique wherein various parts of plant body or the microbes are dissolved in solvents especially water or ethanol. Here, for the plant based extraction, leaves, steam, fruiting body or root are used while in the case of microbes, bacteria, yeast or section of fungus body is used. Among these biological resources, plant and mushroom species are available in large quantity which are important when considering large scale commercial synthesis as biological extraction itself have a low yield of $<15-20\%$.[448] The plant based extracts mainly contains terpenoids, polysaccharide, flavonoids, methanol, amine, polyphenols, alkaloids, phenolic protein, polyold, tannins, chlorophyllin, vitamins and carboxylic compounds while various species of mushroom contains riboflavin, polysaccharides, aldehydes, carboxylic acid, polypeptides, carboxyl and thiol groups (Figure 26) .[230, 449]

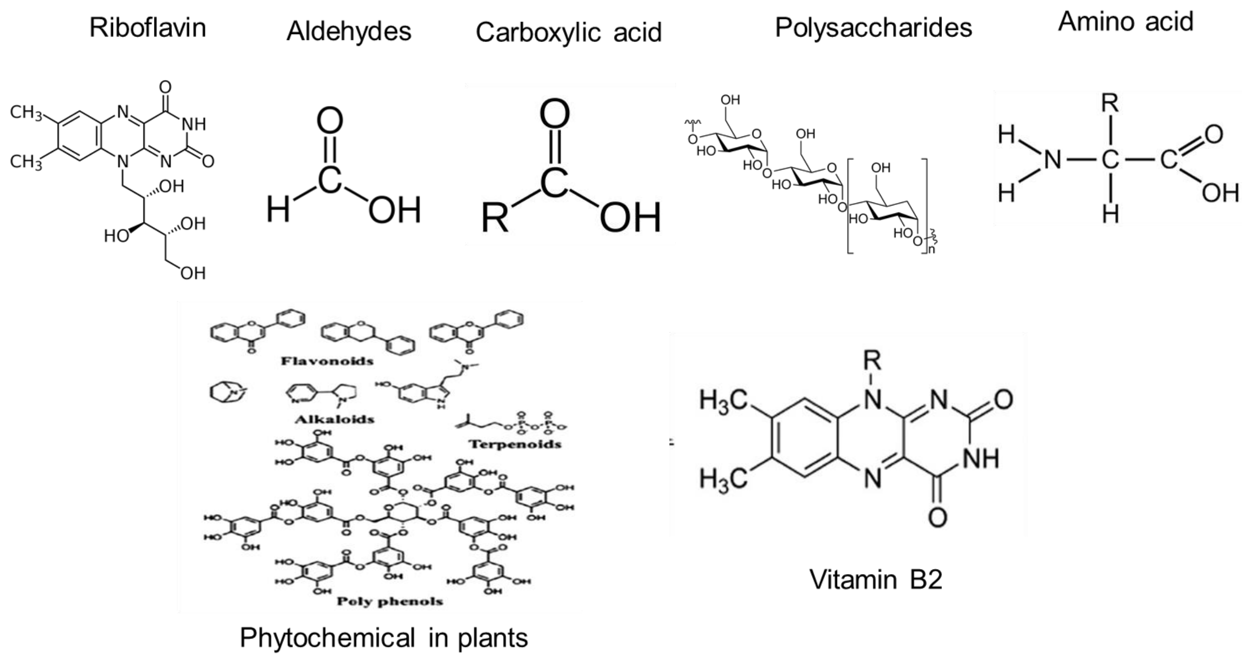


Figure 26. Phytochemicals extracted from plants and mushroom species

Most of these biological extract from colored plant resources can be used directly in the form of optical dyes as they contain anthocyanins, carotenoids and chlorophyll giving various wavelength fluorescence.[108, 149, 166] Other biological extracts from plant and mushroom species consists of carbon based small molecules or polymers which can be used as an organic material for various electrical and optical devices. For example, Ruberene, tetracene, pentacene, tetracyanoquinodimethane are the major carbon based polymer or pi-conjugated molecules which are used in organic field effect transistors as well as organic light emitting diodes.[239, 241] Similarly, nanostructure conjugated polymers and co-polymers like polyaniline, polypyrrole, poly(benzobisimidazobenzophenanthroline), hypericine and polyketones are currently explored for their application in lithium and sodium rechargeable batteries.[242, 450] These compounds can be obtained from natural sources using a green chemistry approach. Furthermore, engineering these biological extracts for synthesizing new compounds and replacing currently existing commercial chemical compounds are new avenues of green synthesis. The detail process diagram for plant/mushroom based biological extraction and application is presented in Figure 27.

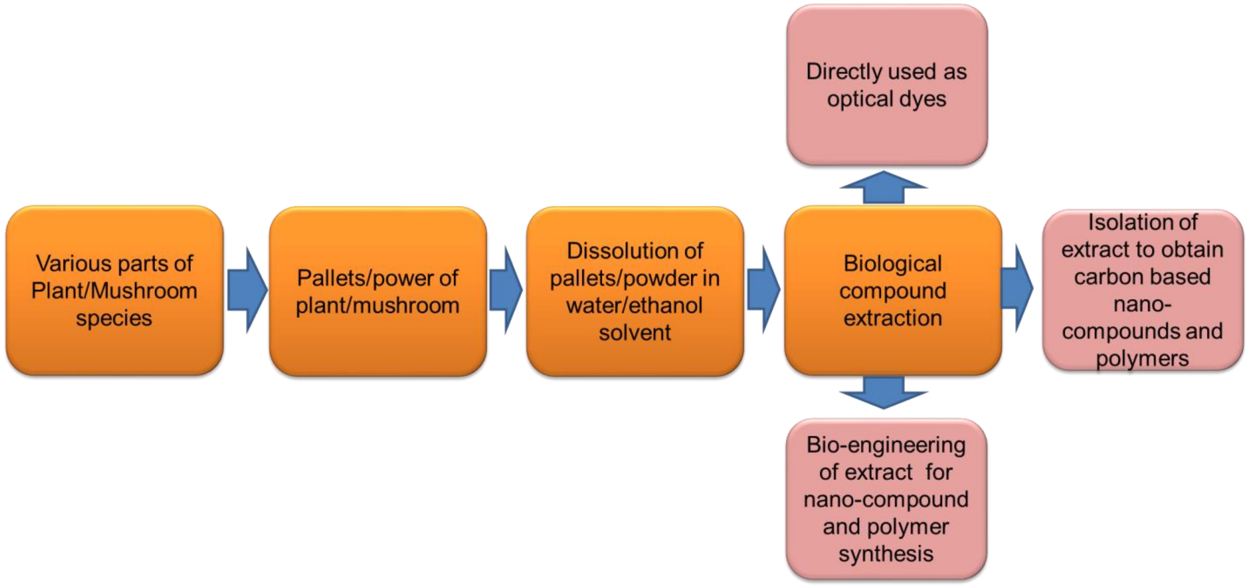


Figure 27. Process diagram for the biological compound extracted from plant and mushroom species and its potential application field

6.3 Biological synthesis of nanomaterial

The biologically extracted phytochemicals from plants and mushroom as described in previous section can induce biological reduction of various mineral/metal salts. This biological reduction can thus produce nanomaterials of various shape, size, dimension and crystallinity. Commonly synthesized nanomaterials from plant and mushroom extract includes silver, gold, selenium, zinc, iron, copper, magnesium, potassium, palladium, cadmium, zinc, various iron oxides, indium oxide, zinc oxide, titanium oxide, copper oxide, cobalt oxide, nickel oxide and chromium oxide, cadmium sulphide, zinc sulphide and composite and alloy of gold and silver and titanium and nickel. Similarly, the mineral/metal salts required from the nanomaterial synthesis can be easily obtained from the natural mineral source which requires simple distillation/fractionation to obtain pure mineral/metal salt. The schematic for the nanomaterial synthesis has been described in Figure 28.

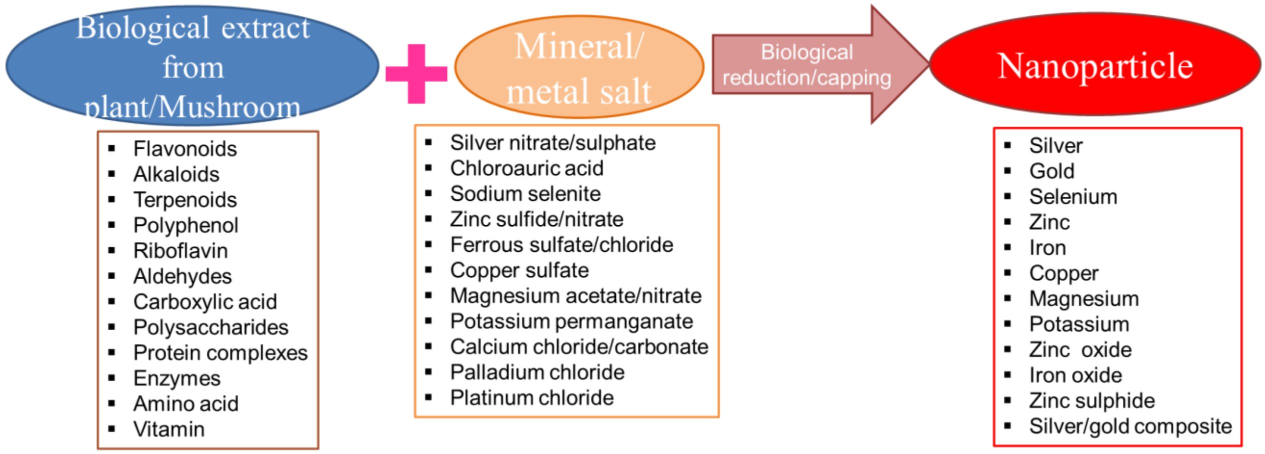


Figure 28. Schematic for the nanomaterial synthesis from plant and mushroom species along with example of various compounds necessary for the process

More importantly, these synthesis produce does not use any external chemical compound for the mineral/metal salt reduction and the reaction can be controlled simply be centrifugation, stirring, heating or under reduced pressure. The details procedure for biological nanoparticle synthesis from plant/mushroom extract is described in Figure 29.

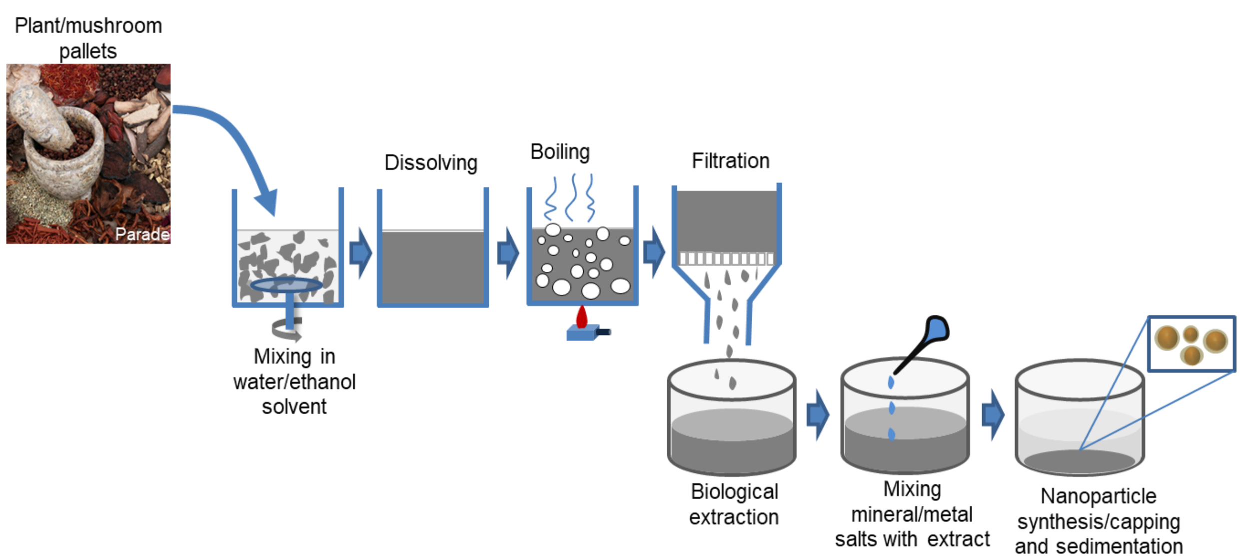
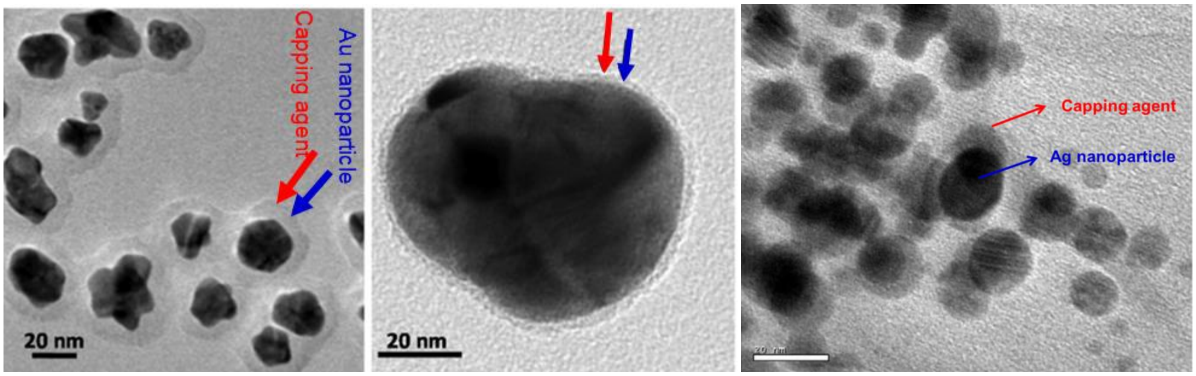


Figure 29. Process schematic for nanomaterial synthesis using plant and mushroom species

The additional advantage of this biological extract based nanoparticle synthesis is the in-situ stabilization of as-prepared nanoparticles due to the capping and functionalization of nanoparticles by the phytochemicals used in the plant extracts (see Figure 30).[246, 451] This thus ensures the long term stability of biologically derived nanoparticles as compared to chemically stabilized which usages complex molecular ligands and organic polymers.



(a) (b) (c)

Figure 30. Biological nanomaterial synthesized from plant (a), (b) and mushroom (c) (Adopted from Ref. 21 and 22)

6.4 Scheme for nanomaterial and nano-compound synthesis

Among various schemes available for synthesizing nanomaterials and nanocompounds the biological reduction using natural solvents like water and ethanol are one of the most convenient and cost effective techniques. At the initial stage of the laboratory preparation in MBUST, this method might be more useful considering the limited resources in adopting advance technology like laser, elevated pressure, low temperature freeze drying and liquid gas for enhancing the product yield and synthesis time. Moreover, the first phase of the experiment is intended to observe the nanomaterial growth dynamics, morphology of the nanomaterials and nano-compounds and the possibility in enhancing the nanoformulation for large scale synthesis and opting the biological extraction to synthesize the nanomaterial can facilitate this at the initial stage of the experiment. Similarly, the low quantity of material using the biological reduction in demonstrating the applications works is still sufficient for experimentation purpose. However at the later stage, incorporation of organic chemistry techniques to enhance the material quantity and growth will be needed in addition to experts and the experiment equipment for conducting the experiment.

6.5 Prospective

The major advantage of this synthesis procedure is that it can produce non-toxic and cost effective biological nano-compounds and nanomaterials. Additionally, the large plant and commercially produced mushroom can serve as the resource for large scale material synthesis. Since this procedure can be used for most of the nanomaterial and nano-compound synthesis, hence the possibilities of using these materials for various application ranging from optics, electronic, biomedical, medicines and agriculture are immense. Furthermore, the possibilities of synthesizing heterostructure nanomaterials in one-step synthesis or integrating the individual nanomaterials into various heterostructures nanomaterials and nano-compounds are further research possibilities that can be explored with optimized synthesis and integration techniques. This is important research prospective when considering the application in electronic/optics devices and in agriculture research for synthesizing of nano-biofertilizer.

Chapter 7. National/international institutions and organizations working on natural product based nanomaterials/technology for future collaborations

7.1 Scheme for collaboration

The nanomaterial based natural product development is new and emerging field of science. This field requires expertise from material science including physics and chemistry to botanist and biotechnologists. Hence research and product development in the field of natural product based nanotechnology requires collaboration and partnership from various field of science including chemical synthesis to device fabrication and characterization. Hence within our proposed natural product research using nanomaterial, there are various potential research collaborations that can be initiated as listed below.

Collaboration for natural product research

1) Prof. Dongwoon Han

   Department of Global Health and Development, Hanyang University, South Korea

   Email: dwhan@hanyang.ac.kr

   Collaboration areas: traditional medicine research for product development, characterization and quality assessment of natural products and natural product commercialization within Korea and Asian countries

   Status: initiated for formal collaboration

2) Dr. Cristian Dal Cortivo

   Department of Agronomy, Food, Natural resources, Animals and Environment, University of Padova, Italy

   Email: cristian.dalcortivo@unipd.it

   Collaboration areas: natural product identification, isolation and characterization

   Status: informally discussed

3) Prof. Jaehong Han

   College of Biotechnology and Natural Resources, Chung-Ang University, South Korea

   Email: jaehongh@cau.ac.kr

   Collaboration areas: natural product synthesis, development and characterization

   Status: informally discussed

Collaboration for chemical engineering of nanomaterials and nano-compounds

1) Prof. Rameshwar Prasad Pandit,

   Department of Chemistry, Sungkyunkwan University, South Korea

   Email: rameshwar.pandit@gmail.com

   Collaboration areas: natural product synthesis, medicinal and heterocyclic chemical synthesis

   Status: communication ongoing, yet to initiate formal collaboration

2) Dr. Niranjanmurthi Lingappan

   Department of Chemistry, University of Maryland, USA

   Email: niranjangowri@gmail.com

   Collaboration areas: organic/inorganic chemical synthesis; nanomaterial synthesis; material characterization; device fabrication based on nanomaterials and nano-compounds

   Status: informal discussion

Collaboration for nanomaterial based product development

1) Prof. Nabeen K. Shrestha

   Department of Energy Materials and Engineering, Dongguk University, South Korea

   Email: nabeenkshrestha@hotmail.com

   Collaboration areas: Chemical synthesis, engineering, analysis; nanomaterial synthesis and nanomaterial based device fabrication and characterization

   Status: communication ongoing, yet to initiate formal collaboration

2) Dr. Suresh Dhungel

   Department of Technology, Nepal Academy of Science and Technology (NAST), Nepal

   Email: skdhungel@hotmail.com

   Collaboration areas: Optical and opto-electronics device fabrication, analysis and characterization

   Status: potential collaborator, yet to discuss for collaboration

3) Prof. Hongyan Yue

School of Material Science and Engineering, Harbin University of Science and Technology, China

Email: hyyue@hrbust.edu.cn

Collaboration areas: Nanomaterial synthesis, characterization and device fabrication

Status: communication ongoing, yet to start formal collaboration

Collaboration for material simulation

1) Dr. Mahesh Bhatta

   Department of Chemistry, Computational Chemistry Lab, University of Ulsan, South Korea

   Email: mbhatt541@gmail.com

   Collaboration areas: Simulation based chemical analysis, simulation based device characterization and analysis

   Status: communication ongoing, yet to start formal collaboration

2) Prof. Madhav Prasad Ghimire

   Central Department of Physics, Tribhuvan University, Nepal

   Email: madhav.ghimire@cdp.tu.edu.np

   Collaboration areas: Nanomaterial simulation and theoretical prospective of new and emerging nanomaterials

   Status: collaboration work initiated, yet to initiate official collaboration

Other potential collaboration for research ideas and characterization

1) Research center for Applied Science and Technology (RECAST)

   Tribhuvan University, Nepal

   Collaboration areas: Natural product extraction and characterization

   Status: potential collaborator

2) Nexus Institute of Research and Innovation (NIRI), Kathmandu, Nepal

   Collaboration areas: product development, characterization and research ideas support

   Status: potential collaborator

Among these potential list of collaborators for natural product based nanomaterial research in Madan Bhandari University of Science and Technology (MBUST), Prof. Dongwoon Han has been formally requested for collaborating with MBUST. We have formally requested Prof. Han to collaborate and support on the following research areas:

1. Mushroom (Oyster, Buttom and Shitake, Cordyceps) cultivation and production
2. Nutraceutical and food supplement products based on Aegle marmelos, Choerospondias axillaries, Curcuma longa, Mahonia napaulensis, Taraxacum officinale
3. Extraction, analysis and processing of medicinal plants and herbs like rhodendron, orchid, turmeric, marijuana and cordyceps for synthesis of optical dyes and development of antioxidants supplements and anticancer drugs
4. Nanomaterials and nanocompounds extraction and synthesis from agricultural and forest waste for production of organic fertilizer and biomedical compounds

7.2 Conclusion

These collaborative initiations are based on the focused areas of MBUST in research and academics. While some of these collaboration have been informally initiated, a formal working modality will be designed after the successful initiation of academic and research programs in MBUST. Regarding other potential collaborations, informal talks have been initiated with the respective professors and the academic institutions. These initiations will continue until the formal opening of MBUST academic programs.

Chapter 8. Potential areas/fields of introduction of nanotechnology for biomedical, technological and agricultural application in relation to the natural products

8.1 Introduction

Madan Bhandari University of Science and Technology Development Board (MBUSTB) have prioritized forest bio-material engineering, organic agriculture and artificial intelligence as the major academic programs. These academic programs are mostly research based and will comprise of modern and industrial research. Forest biomaterial engineering and organic agriculture also consists of nanotechnology, as part of their research topics. Moreover, these nanoparticle research will mostly utilize natural product and natural resource as their source materials. Mainly the forest and agricultural resources will be used for synthesis of various nanomaterials, nanofibers, polymers and nano-compounds for developing product on technology, agriculture and biomedical fields. Hence based on these, the areas/fields within nanotechnology that can be utilized for research purpose in MBUST are mainly technological, agricultural and biomedical.

8.2 Technology (optical and opto-electronics material)

i) Development of optical active nano-compounds and nanomaterials based dyes from flowering species like rhodondendron and orchid

ii) Development of optically active fluorescent nanomaterials from turmeric plant species

iii) Cellulose nanofibers and cellulose nanomaterial synthesis from wood-derived pulp for application in filtering devices, electronic devices, and sensing applications

iv) Development of weak acids from fruits and plant species for defect healing in energy storing and nano-electronic devices

v) Development of nano-composites based on carbon and cellulose nanomaterial derived from plant sources for its application in automobile and metal industries

vi) Organic semiconductors derived from plant based resources for application in electronics and light emitting diodes

vii) Development of biomaterial coating using plant based phytochemicals to increase the stability of nanomaterials

8.3 Agriculture (nano-biofertilizer)

i) Nanomaterials synthesis from plant extracts for its application in organic and inorganic fertilizer

ii) Development of nanoparticles form of spent mushroom substrates for its use in organic fertilizers

8.4 Biomedical (pharmaceutical and daily wellbeing products)

i) Nanomaterials and nano-compounds synthesis from plant extracts for its application as antimicrobial, antiviral, anticancer, antioxidant agents in pharmaceutical products

ii) Nanomaterials and nano-compounds synthesis from plant extract for its application in bio-cosmetics.

iii) Development of gas barrier films for food preservation using plant derived cellulose nanomaterial

iv) Development of nanomaterials and nano-compounds as a drug delivery agent for targeted drug delivery

v) Development of bio-catalyst nanomaterials and nanofibers from plant resources

8.5 Conclusion

The nanotechnology assisted research fields using natural products as the source materials are one of the emerging research areas. It is mainly due to the non-toxic and green materials that can be synthesized using natural products. Moreover, the use of non-toxic nanomaterial in the modern technological and biomedical devices and in agriculture are also one of the sustainable technology that is highly required in modern research and industries. Moreover, there are various new and emerging research field being developed with the aid of bio-nanomaterials like organic solar cell, organic energy storage devices, natural products based medicines and organic displays. These fields is expected to increase continuously as the research and finding in natural products research have shown high prospective for application and industrialization.

Chapter 9. Potential research projects based on nanotechnology for development of natural products, including technology development, proto-type development, patenting, production and marketing

9.1 Introduction

The nanotechnology research covers a broad range of application areas. Natural product based nanomaterials and nano-compounds are new and increasing research avenue within nanotechnology with focus on green and sustainable technology, organic agriculture development and biomedicine and biomedical applications. The natural product research group in Madan Bhandari University of Science and Technology (MBUST) will also adopt this green and sustainable research field utilizing the natural resources in Nepal. The main research projects will thus focus on utilizing nanomaterials synthesized from natural products for development of products in the field of technology, agriculture and biomedical fields.

9.2 Synthesis of nanomaterial and nano-compounds from natural products using green chemistry

Nanomaterial and nano-compound synthesis using natural resources is one of the important research avenue in green chemistry. The quality, quantity, size, morphology and the economic cost of nanomaterial synthesis determines the application prospective of nanomaterials. Until now various metallic, semiconducting and mixed heterostructure nanomaterials have been synthesized using natural products. However, the low quantity of nanomaterial and the non-uniform size distribution of nanomaterials obtained using biological synthesis techniques are still a major concerns. Similarly, many of the biological synthesis procedures utilize inorganic chemicals to enhance the yield and the stability of nanomaterials. Hence the major research areas within the natural product based nanomaterials synthesis for technology and proto-type development are:

- Designing complete green nanomaterials and the synthesis technology using universal solvents like water and organic chemicals
- Developing technology for increasing the yield in natural product extraction
- Designing low cost phytochemical extraction procedures using grinder, pressure, temperature, and physical rotation
- Developing green and stable phytochemicals for functionalization and capping of bio-nanomaterials

9.3 Synthesis of optical and opto-electronics material and devices using natural product based nanomaterials and nanocompounds

Plant based phytochemicals are an important source of obtaining green nano-compounds and nanomaterials. The various parts of plant like leaves, flowers, roots, bark, and steam can be utilized as a source for obtaining new chemicals, nanomaterial, polymers and products. Moreover, the color parts of these plants also can be utilized for the synthesis of optical nanomaterials and nano-compounds. Similarly, based on the phytochemical composition and its chemical engineering various polymer, fiber, nanomaterials and nanocomposites can be developed for various application like electronics, opto-electronics, energy storage, energy production and sensing. Some of these research prospective in this field utilizing the Nepalese local resources are highlight below:

- Development of optical active nano-compounds and nanomaterials based dyes from flowering species like rhodondendron and orchid
- Development of optically active fluorescent nanomaterials from turmeric plant species
- Cellulose nanofibers and cellulose nanomaterial synthesis from wood-derived pulp for application in filtering devices, electronic devices, and sensing applications
- Development of weak acids from fruits and plant species for defect healing in energy storing and nano-electronic devices
- Development of nano-composites based on carbon and cellulose nanomaterial derived from plant sources for its application in automobile and metal industries
- Organic semiconductors derived from plant based resources for application in electronics and light emitting diodes
- Development of biomaterial coating using plant based phytochemicals to increase the stability of nanomaterials

9.4 Synthesis of nano-biofertilizer using biologically synthesized nanomaterials

Forest and agriculture waste are green biological resources that have been used for the synthesis of organic compost and manure. However the low nutrient composition in such compost and manure limits the large scale application. At present, the new research techniques to incorporate various nanomaterials as a source of micronutrients in the fertilizer have shown great prospective in increasing the nutrient composition in organic fertilizers. These nanomaterials as source of micronutrients can be synthesized using plants based phytochemical. Various plant resources can be used for synthesis of various nanomaterials with different morphology, size and physical forms. These nanomaterials can later be inoculated in the animal manure and organic compost to increase the nutrient composition and yield. Hence the research topics under the nano-biofertilizer can be highlighted as:

- Designing phytochemical based metallic and metal-oxide nanomaterial synthesis procedures
- Estimating the size, morphology, stability and functional properties of green nanomaterials for inoculation in organic fertilizer and increasing the absorption in soil
- Developing nanomaterial based composite by retaining the size and physical properties of nano-biomaterial

9.5 Research and development of pharmaceuticals and daily wellbeing products using biologically synthesized nano-compounds and nanomaterials

Green chemicals and nanomaterials based drugs are one of the prime alternatives against adversity caused by pharmaceuticals drugs. Similarly, biologically synthesized nano-compounds and nanomaterials are being used for disease research and targeted drug delivery. Similarly, the cosmetic and daily well-being products are also slowly shifting towards bio-based nanomaterials. Hence the research prospective within the field of pharmaceuticals and daily well-being products can be highlighted as:

- Developing nanomaterials and nano-compounds based antimicrobial, antiviral, anticancer, antioxidant products using biological resources
- Nanomaterials and nano-compounds synthesis from plant extract for its application in bio-cosmetics.
- Development of gas barrier films for food preservation using plant derived cellulose nanomaterial
- Development of nanomaterials and nano-compounds as a drug delivery agent for targeted drug delivery
- Development of bio-catalyst nanomaterials and nanofibers from plant resources

9.6 Conclusion

There are various opportunities within the newly developed field of nanomaterial and nano-compound synthesis and engineering using natural products. From developing technology for the material synthesis to designing proto-type for product development, the natural product based nanomaterials and nano-compounds are slowly being commercialized in major economic field like technology, agriculture and pharmaceuticals. Hence, the designing of green nanomaterial synthesis procedure utilizing the physical mediums like pressure, temperature, mixing and grinding to increase the product yield can be developed as a universal proto-type technology that can be utilized in the phytochemicals extraction and green nanomaterials synthesis industries. There also exist various possibilities in designing new techniques in increasing the yield of green nanomaterial and nano-compound synthesis that can also be developed as a patent. The prospective of this biologically synthesized nanomaterials and nano-compounds in optical, electrical, optoelectronic, energy storage, energy production, organic agriculture, chemical sensing, biomedical and pharmaceutical are slowly developing as industrial products and the product development research on these fields can thus lead to development of various new and emerging technology. Moreover, the technology development, proto-type development is ultimately aimed for patenting and product development. The universally acceptable technology for the nanomaterial synthesis can also lead to product marketing and eventually developing industries based on the new products.

Chapter 10. Design of Master's and PhD level course in Madan Bhandari University of Science and Technology (MBUST) for research on natural products of Nepal

10.1 Outline

Madan Bhandari University of Science and Technology (MBUST) have prioritized forest bio-material science and engineering, organic agriculture and artificial intelligence as the major academic programs. All these three different fields are inter-related by research on natural resources and the natural resource based product development. These three different fields were developed after rigorous discussion with experts, entrepreneurs and stake holders working on the specific fields. The program design for forest bio-material science and engineering, organic agriculture and artificial intelligence were led by international academic experts working on the specific fields. As a MBUST consultant, we provided valuable suggestion and feedbacks during the design of the program.

10.2 Support design of Master's and PhD level course in MBUST

The main feedback as a nanotechnology consultant during the design of academic program were:

i) Since the program also envisions material science based research using forest products, I would recommend to have a strong course of material science (including aspects of low dimensional materials, especially carbon based and their synthesis and application) in the beginning of both Masters and PhD. This is also important because most of the Physics and engineering courses in Nepal lack material science syllabus. Hence those students who come to MBUST should be first introduced with material science and material chemistry knowledge along with its aspect/prospective in modern research/technology. In the later semesters we can move into fundamental of forest, forest biomaterials, biomass conversion techniques and sustainable bioproducts. (Feedback to Prof. Ning Yang)

ii) Since the masters and PhD courses are research based and the students should be familiar with many characterization techniques and tools. Hence the current syllabus proposed should also incorporate courses on material characterization with the knowledge on working principal of characterization tool/equipments. This can also be incorporated in the practical courses for Masters students but for the PhD students, a subject course would be much helpful. This way we can also prepare technical manpower to handle the research facilities which otherwise need permanent experts. (Feedback to Prof. Ning Yang)

iii) The importance of organic nanofertilizer is increasing and this should be included as a research component in organic agriculture program. The use of biologically synthesized nanomaterials can act as a nutrient source in organic fertilizer and also regulate the major nutrient consumption by the plants. Hence the organic research program should include bio-nanofertilizer synthesis and development as a academic content as well as a research project. (Feedback to Prof. Andre Ronald Van Amstel)

iv) The plant derived chemical and compounds are large in numbers. Experimentally synthesizing and characterizing each compound for the application purpose might take years to complete. Hence using artificial intelligence and machine learning techniques we can develop a model based on the available data to predict the natural chemical and compound available in the plant and their application prospective. (Feedback to Prof. Suresh Manandhar)

10.3 Formulation of topics for PhD and Master's degree research

Within the programs designed in MBUST following are the potential topics for PhD and Master's degree research program:

i) Synthesis of green nanomaterial and nano-compounds using forest and agricultural waste

ii) Synthesis of optically active nano-compounds and nanomaterials based dyes from flowering species like rhodendron and orchid and herbal plant species like turmeric

iii) Synthesis of weak acids from fruits and plant species for defect healing in semiconductors materials

iv) Fabrication of organic semiconductors using pant derived nano-compounds for application in display devices, solar cell, supercapicators and light emitting diode

v) Developing Cellulose nanofibers and cellulose nanomaterial synthesis from wood-derived pulp for application in filtering devices, electronic devices, and sensing applications

vi) Synthesis of nano-composites based on carbon and cellulose nanomaterial derived from plant sources for its application in automobile and metal industries

vii) Synthesis of nano-biofertilizer using biologically synthesized nanomaterials as a micronutrient source

viii) Design biomedical products using green nanomaterials synthesized using forest and agricultural waste

10.4 Conclusion

Natural product based research at present in MBUST is envisioned as an independent research unit. Hence most of the work carried out in natural product research group is focused on utilizing the high value natural resources in Nepal that have potential for product development. Hence there is no specific course that has been proposed for natural product based research at present, especially focusing on nanomaterial and nanotechnology. However, the forest bio-material and organic agriculture are the main courses that is proposed at present in MBUST. Based on this, various suggestion described above were presented to the respective professors designing the curriculum design and many of these suggestion has already been incorporated in the finalized coursework.

Similarly, the proposed topics for masters and PhD are based on the utilization of natural products in Nepal for developing organic dyes, nano-biofertilizers and organic nanomaterials and nano-compounds for various electrical and optoelectronic purposes like energy storage, energy generation/transport, sensors and nano-filter devices. Moreover, the bio-nanomaterial and nano-compound synthesis is another important research avenues considering the various applications listed above.

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