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Phytonanotechnological perspectives and biological activities in *Curcuma* species

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Abstract

Natural resources are always been an essential and invaluable source for the novel chemical entities having therapeutic activities. The structural changes in the chemical compounds are mainly responsible for the vast pharmacological and other biological properties. The upsurge need for the more effective and highly potent drugs for various agents such as antimicrobial, antidiabetic, anticancer, antidiarrhoeal, anti-inflammatory, antiarthritic, *etc*. Plant based nanotechnology driven drugs, phytonanotechnology materials have been developed and integrated into different applications such as industrial, biomedical and agricultural for better usage in the disease prevention, treatment and management having good efficacy. The utility of these plant based nanomaterials due to their unusual characteristics may resolve several challenges in the drug delivery and exhibit various pharmacological and biological activities. The synthesis by physical and chemical methods are expensive and unsafe, therefore, green synthesis of nanoparticles to be utilized with the aid of medicinal plants, bacteria, fungi which are novel ecofriendly techniques. Zingiberaceae family comprises about 50 genera usually found throughout the warm regions of both the hemispheres. The *Curcuma* species characterize by the presence of curcuminoids, turmerones, volatile oils and oleoresins of export value. *Curcuma* species has acquired great importance all over the world due to wide medicinal activities such as antimicrobial, antiulcer, antidiarrhoeal, antiaging, antialzheimer, antioxidant, antidiabetic, anti-inflammatory. Various species of *Curcuma* has been extensively reported for their pharmacological activity. These species are effective against several diseases and also in remedies used by tribal.

1. Introduction

Currently applications in the usage of plant based nanotechnology systems such as phytonanotechnology has gained importance. It allows target-site specific drug delivery through phytonanomaterials to agricultural fields and other plants. This causes enhanced functions of plants and environment friendly and resistance to pollution.

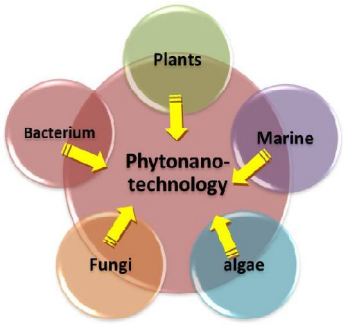

Figure 1: Sources of phytonanotechnology.

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Phytonanotechnology has influenced scientific fraternity to do more studies in this direction. Phytonanotechnology products can be obtained from different resources such as plants, bacterium, marine, fungi, algae, *etc*., as depicted in Figure 1 which sources yields variety of products illustrated in Figure 2 (Li and Yan, 2020).

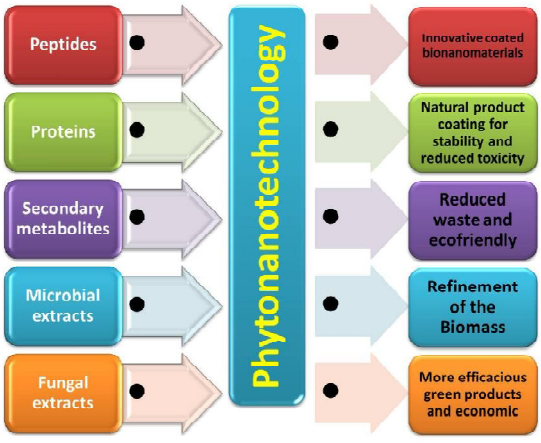

Figure 2: Phytonanotechnology sources yields variety of products.

Phytonanotechnology has also become popular in the field of nanofertilizers, nanoinsecticides and nanopesticides due to the inherent benefits and nanoscale size effects which are capable of better uptake of minerals, insecticides and pesticides by the plants.

(Chhipa, 2017; Kah *et al*., 2018). Nanotechnology has been used in case of turmeric to produce more efficacy in the phytonanomaterials products from different *Curcuma* species particularly in *Curcuma longa* L. Turmeric is very important spice in India which produces nearly 80 % of the whole world's consumption and largest producer and exporter of turmeric under spices and condiments. Several species of *Curcuma* are native to India, *Curcuma longa* (Watt, 1872) among one of them. Rhizome of turmeric (*Curcuma longa*) contains a potent polyphenol compound curcumin (Rasheed *et al*., 2017) which possess potent anticancer properties showed in plethora of human cancer cell line and animal carcinogenesis models. The clinical application of curcumin efficacious agent in cancer and other diseases has been reduced due to its poor aqueous solubility, and minimal systemic bioavailability. Nanoparticle-based drug delivery approaches for rendering hydrophobic agents like curcumin dispersible in aqueous media, thus avoiding the drawbacks of poor solubility.Thus, nanotechnology enhances the potential properties of turmeric and increases the possibilities for the application of its components.

Curcuminoids are one of the important bioactive secondary metabolite present in *Curcuma* species which prevents the spoilage of fat foods during storage (Revarkar and Sen, 1975). And also used in the preparation of pickles (Govindarajan and Stahl, 1980). *C. longa* essential oils are used in the perfumery, cosmetics and soap industry (Ramachandraiah *et al.,* 1998). The food regulation Act 1996, part III schedule-5 confirms the usage of curcumin in various items in U.K. (Henry, 1998). Anticancerous drug dose level of curcumin ranges from 5-200 ppm (Chen and Huang, 1998). Chemo protective role of curcumin in human colon cancer was studied (Kawamori *et al*., 1999). Essential oil of turmeric is found to be effective in ayurvedic medicine of Indian system (Marwah and Shetty, 2000). In food industry, turmeric powder is used in Asian countries for making vegetables and meat preparations (Sasikumar, 2005). *C.longa* is the major source of curcuminoids and volatile oils (Jayaprakasha *et al*., 2002). *Curcumin* also inhibits Sperm motility and acts as novel intravaginal contraceptive (Rithaporn *et al*., 2003), antidiabetic activities (Suryanarayana *et al*., 2003). The crude form of turmeric powder, fresh ground turmeric and the water, ether, chloroform and methanolic extracts plays an important role in the bioprotective activity of various ailments. *Curcuma longa* consists 3-8% of curcuminoids as a major content than in other species (Varghese, 1999).

Out of 10 *Curcuma* species, *Curcuma amada* and *Curcuma zedoaria* are distributed throughout India in the wild and in cultivation whereas the four species *C. aeruginosa, C. brog, C. caesia* and *C. sylvatica* distributed only in wild conditions along northeastern parts of India. *C. malabarica* and *C. aromatica* distributed in South India while *C. rakthakanta* and *C. harita* are distributed throughout Kerala (Velayudhan *et al*., 1999). *Curcuma neilgherrensis* is reported from Andhra Pradesh from araku valley and seshachalam hill ranges of tirumala and talakona along the eastern ghats (Pullaiah, 1997). Turmeric has been used as medicine and coloring agent. It acts as effective in wound healing and also against stomach ache, flatulence, poisonous reptile bites, ulcers, common cold, pimples and bronchitis, anti-inflammatory, antidiabetic, sinusitis, *etc*. (Sasikumar, 2005).

In the traditional veterinary medicine, also *Curcuma* plays an important role on the rural poultry and to treat skin diseases of camel and buffalo (Chhabra *et al*., 1994), mastitis in cattle (Joshi *et al*., 1996). *C. aromatica* extracts against cattle anti-inflammatory activity (Jangde *et al*., 1998). Turmeric poultice is applied on broken legs of chicken and domestic animals (Mandal and Chauhan, 2000); also used to cure raniket disease of birds, prevent hair fall, scabies, heal cuts and wounds ring worm infection, itching, eczema, boils, urticaria and chronic skin eruptions of domestic animals (Sharma and Joshi, 2004).

Curcumanol compound yielded from hydroalcoholic extract of *C.zedoaria* is proved to use as analgesic (Navarro *et al*., 2002). *C. caesia*, *C. amada* and *C. longa* rhizome consist four secondary metabolites only (Jose and Thomas, 2014; Donipati and Sreeramulu, 2015; Pawar *et al*., 2015). In recent studies, oil extraction from the *C.longa* leaves yielded terpenoids compound which also used as biofuels an alternative to that of petrol (Gantait *et al*., 2011).

Macro and microscopic studies of *C. neilgherrensis* reveals that the rhizome in conical shape, brownish with mild aromatic flavor to that of *C.caesia*. But, it is different from other *Curcuma* species in having fusiform long tuberous roots, with secondary branching. Saponins are present only in *C. neilgherrensis* whereas in other *Curcuma* species they are absent. Hence, each *Curcuma* species is having specific pharmacognostic characters to be identified in its quality and quantity in the drug formulations and also to check the adulterations (Chitra and Thoppil, 2002; Shyam *et al*., 2013; Prakash *et al.*, 2011).

1.1 Ethnomedicinal uses of *Curcuma* species

Table 1: Ethnomedicinal uses in different part of the *Curcuma* species and their medicinal properties

Plant name	Medicinal uses	Part used	Reference
Curcuma amada	Anti-inflammatory, bruises, sprains, wounds, skin diseases, bronchitis, asthma, diarrhoea; Antimicrobial and antioxidant; CNS Depressant and analgesic activity; Antiallergic, Brine-shrimp lethal; Platelet aggregation inhibitory, Cytotoxicity; Hypoglycemic; Anti-hyperglycemic	Rhizomes	Mujumdar *et al*., 2000; Joy *et al*., 2001; Ankli *et al*., 2002; Mujumdar *et al*., 2004; Krishnaraju *et al*., 2006; Policegoudra and Aradya, 2008; Syiem *et al*., 2010
Curcuma aromatica	Antitumor, antidementia, bruises, sprains, bronchitis, cough and skin eruptions, antiallergy	Rhizomes	Ozaki., 1990; Khar *et al*., 1999; Lim *et al*., 2001; Joy *et al*., 2001; Ram *et al*., 2003

Curcuma aromatica *Curcuma amada* *Curcuma zedoaria*	Intestinal worms	Rhizomes	Joy *et al.*, 2001
Curcuma amada and *Curcuma caesia*	Anti-inflammatory, antimicrobial	Rhizomes	Gill *et al.*, 2011
Curcuma aeruginosa, *C. brog* *C. malabarica* *C. rakthakantha* *C. sylvatica*	Antioxidant	Leaves	Angel *et al.*, 2012
Curcuma aeruginosa	Antinociceptive, antipyretic and anti-inflammatory, cough, asthma, rheumatic conditions	Rhizomes	Reanmongkol *et al.*, 2006; Nasrullah *et al.*, 2010
Curcuma angustifolia	Leprosy, asthma, anemia and leukoderma, pneumonia, cough, asthma	Rhizomes	Kirtikar and Basu, 1987; Chourasia, 2006
Curcuma caesia	Sprains and bruises, snake and scorpion bites	Rhizomes	Tag *et al.*, 2007
Curcuma longa + *Zingiber officinale*	Analgesic, antibacterial, antioxidant, expectorant	Rhizomes	Mujumdar *et al.*, 2000
Curcuma longa	Hypoglycemic, hypolipidemic and antioxidant	Rhizomes, Whole plant	Hussain, 2002
Curcuma longa and *Zingiber officinale*	Analgesic, antibacterial, antioxidant, expectorant	Rhizomes	Singh *et al.*, 2011
Curcuma longa, *Zingiber officinalis*, *Zingiber zerumbet*	Anthelmintic	Rhizomes	Raul *et al.*, 2012
Curcuma longa	Anti-inflammatory, hepatoprotective, antimicrobial, wound healing anticancer, antitumour and antiviral, antiulcer, antimicrobial, anti-inflammatory	Rhizomes	Ross, 1999; Ghongane and Rahul, 2011; Khan *et al.*, 2013
Curcuma *neilgherrensis*	Skin diseases, throat infections, sneezing, respiratory disorders, asthma	Flowers	Kirtikar and Basu, 1935; Rathnam and Raju, 2005
Curcuma *rakthakantha*	Diarrhoea, antidiabetic, antihyperglycemic and antioxidant activity	Rhizomes	Inthirakanthi *et al.*, 2013
Curcuma xanthorrhiza	Liver disorders, constipation, bloody diarrhoea, dysentery, haemorrhoids, skin eruptions; antidiabetic activity	Rhizomes Leaf	Hwang *et al.*, 2000; Adnyana *et al.*, 2013
Curcuma xanthorrhiza and *Curcuma domestica*	Antioxidant, anti-inflammatory	Rhizomes	Waras *et al.*, 2012

1.2 Antimicrobial activity

Studies on antibacterial activity for nanoparticles of *C. longa*, *C. zedoaria*, and *A. sativum* extract on chronic respiratory disease (CRD) infected chicken by *M. gallisepticum* and *Escherichia coli* carried out *in vivo*. The morphology of turmeric, zedoary, and garlic extract nanoparticle was smooth surface and sphere shapes as shown in Figure 3 (Handharyani *et al.*, 2020). *In vivo* studies of nanoparticle extract combination of turmeric, zedoary, and garlic showed improved in growth and performance of chicken with recovery in clinical and pathological changes of CRD complex infection.

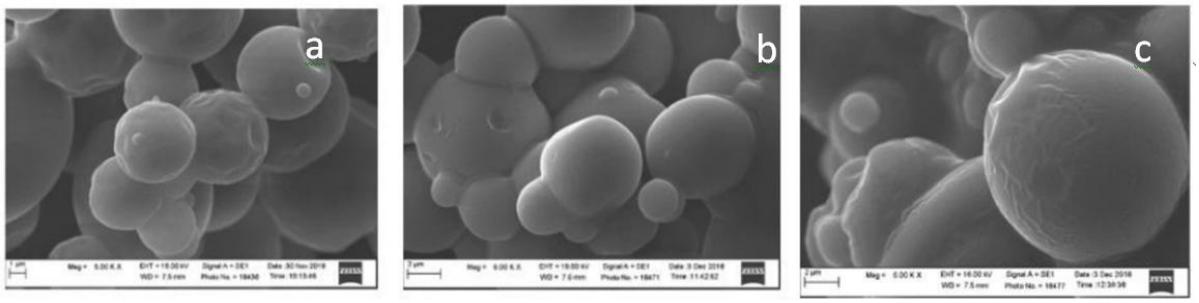

Figure 3: Morphology of nanoparticle under scanning electron microscope (SEM) analysis of (a) turmeric, (b) zedoary, and (c) garlic (Photo Source: Handharyani, *et al.*, 2020).

An ecofriendly novel method for silver nanoparticle was synthesized using rhizome extract of *Curcuma amada.* The green synthesized silver nanoparticle showed excellent antimicrobial activity and considerable zone of inhibition against both gram-negative and gram-positive bacteria and fungi (Khairunnisa, and Anjana, 2018). Rhizome extracts of *C. neilgherrensis* consists a good number of secondary metabolites like alkaloids, flavonoids, phenols, steroids, tannins, lignins, indoles, glycosides, carbohydrates, proteins, amino acids proved effective antibacterial activity with alcohol and aqueous extracts at 10 mg/well with MIC 0.078 mg on *Staphylococcus aureus* and *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* are inhibited equally to that of standard drug ampicillin due to the presence of *p*-hydroxy benzoic acid, vanilic acid, scopoletin, pincarvone, 3-carene, terpinol, α-thujene, β-pipene and α-amorphene compounds. Whereas, *C. zedoaria* and *C. malabarica* rhizome, hexane and acetone extracts in 1:1 ratio combination against six bacterial and two fungal strains exhibited effective activity than other extracts and *C.malabarica* is most efficient activity against *S.aureus* than *C.zedoaria* (Wilson *et al*., 2005). Rhizome methanolic and alcoholic extracts inhibit anti-methicillin-resistance *Staphylococcus aureus* as that of *C.longa* apart from other bacterial strains to that of *C.longa*, *C.zedoaria* and *C.xanthorrhiza* (Kim *et al*., 2005; Mary*et al*., 2012; Yasodamma *et al*., 2013).*Curcuma neilgherrensis* can be used to synthesize nanoparticles using green chemistry methods for various applications. The ZnO nanoparticles were synthesized using *Curcuma neilgherrensis* methanolic extract of leaf and found to possess alkaloids, flavonoids, steroids, phenols, tannin and carbohydrates which showed good antibacterial activity (Parthasarathy, 2017).

Antifungal activity on *Staphylococcus aureus* and *Bacillus subtilis* strains with methanolic and alcoholic extracts of leaf and rhizome of *C.neilgherrensis* proved most effective to that of the control drug nystatin and the MIC values on *C.albicans* ranges from 0.156 to 2.5 mg and on *A. niger* ranges from 0.312 to 2.5 mg. The lowest concentrations observed with methanol and alcoholic extracts of both leaf and rhizome extracts at 0.156 mg on *C. albicans* due to the presence of phytoconstituents sinapic acid, melilotic, cinnamic acids, pinocarvone and terpineolcompounds. Antifungal activity with isolated compounds of *C. longa* and *C. xanthorrhiza*, *C. malabarica*, *C. zedoaria* is equal to that of *C. neilgherrensis* crude extracts and volatile oils curcuminoids shows most promising activity (Singh and Jain, 2011; Wilson *et al*., 2005).

1.3 Antiulcer activity

Effective antiulcer activity was observed with aqueous rhizome extracts of *C. neilgherrensis* at 500 mg/kg with ulcer index and ulcer protection and also decreased levels of gastric juice, free and total acidity to that of the pyloric ligated ulcer induced rats and equal when compared to the standard drug, omeprazole treated rats. pH also maintained to that of normal rats. Qualitative analysis of phenols, flavonoids and anthocyanidins of *C. neilgherrensis* of various phytoconstituents which also helpful in regulating ulcer activity. Caffeic acid (leaf and rhizome) may protects the intestinal carcinogenic activity (Tonari *et al*., 2002; Yasodamma *et al*., 2014). Myricetin (leaf) plays an important role in the inhibition of tumors and lowers the risk of prostate and pancreatic cancer (Knekt *et al*., 2002). Apigenin (leaf) antitumorous (Si *et al*., 2009); kaempferol (leaf) strong antioxidant prevents formation of cancer cells as chemopreventive especially bone (Andlauer, 1998); tumour (Pang *et al*., 2006). Cyanidin (rhizome) has potent antioxidant activity and reduces the risk of leukaemia, colon, skin and prostate cancer (Sasaki *et al*., 2007). Antioxidant and anticancer activities of *C.neilgherrensis* methanolic leaf and rhizome extracts may show the cytoprotective effects in inhibiting the growth of MCF-7 (breast), Hela (cervical) and A-549 (lung) cancer cell lines (Rubalakshmi and Karmegam, 2011). *C. longa* ethanol extracts 500 mg/kg; *C. zedoaria* root extracts at 200 mg/kg, and also ethanolic extracts of *C. caesia* at 500 mg/kg (Das *et al*., 2012). Turmeric extracts possess highly significant antioxidant activity than α-tocopherol. It is found that α- tocopherol can mitigate stress-induced ischemia in tissues (Toda *et al*., 1985).

1.4 Antidiarrhoeal activity

Methanolic rhizome extracts of *C.neilgherrensis* showed effective at 1000 mg/kg b.wt.for antidiarrhoeal activity may be due to the presence of a wide range of phytoconstituents like terpinoids, tannins, phloroglucinol and *m*-hydroxy benzoic acid, curcumol and caryophyllene compounds (Chaithra and Yasodamma, 2015). Castor oil produces diarrhoea due to its most active metabolite ricinoleic acid by hypersecretory response, which stimulates peristaltic activity in the small intestine, leading to changes in the electrolyte permeability of the intestinal mucosa. Castor oil also stimulates the release of endogenous prostaglandins E and F which cause stomach cramp and diarrhoea due to the effect on the smooth muscle and secretion (Saha and Paul, 2012). *C.longa* rhizome aqueous extract showed effective at 200 mg/kg b.wt. on both gastrointestinal motility and experimentally induced diarrhoea in mice (Owolabi *et al*., 2012).

1.5 Anti-inflammatory activity

Anti-inflammatory activity of *C. neilgherrensis* rhizome methanolic extracts at 250 mg/kg b.wt. more effective against inflammation to that of the standard drug diclofenac at 100 mg/kg b.wt.due to the presence of caffeic acid, apigenin, quercetin, curcumin, eucalyptol and terpineol compounds. Rhizome and leaf extracts proved non-toxic to that of *C.amada* and *C. longa* also proved equally effective anti-inflammatory drugs (Sudharshan *et al*., 2010; Kaushik and Jalapure, 2011), whereas *C.aeruginosa*, *C.aromatica* are showed toxicity effects but anti-inflammatory activity at sub-lethal doses. The presence of quercetin in *C. neilgherrensis* reduces inflammation and flavonoids presence showed the inhibitory action against various enzymes as protein kinase, protein tyrosine kinases and phospholipase A (Middleton, 1998).

C. longa anti-inflammatory activity may be due to the presence of curcumin and effective inhibition on phosphorlipase, lipoxygenase cycloxygenase, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, peroxidase, tumor necrosis factor (TNF) and interleukin -12 (IL- 12). Curcuminoids are the major constituents of turmeric along with bis-demethoxy curcumin and demethoxy curcumin possess antioxidant, anti-inflammatory, antiviral and antifungal activities (Chainani *et al*., 2003).

1.6 Antiarthritic activity

Effective inhibition of arthritic effect with rhizome extracts of *C.neilgherrensis* against acetic acid induced analgesic and against complete freund's adjuvant (CFA) induced arthritis rats. Both aqueous and methanol crude extracts at 1000 mg/kg b.wt.showed

effective results to that of the control rats and also with the standard drug diazepam and diclofenac treated rats. The rhizome crude extracts of *C. neilgherrensis* shows the presence of phytoconstituents like delphinidin, apigenin, quercetin, caffeic acid and essential oils like terpineol, α-thujene, n-heptane, curcumol, eucalyptol, 3-carene and pinocarvone compounds acts as effective antiarthritic drugs (Yasodamma and Chaithra, 2016).

Antiarthritic activity also observed by the application of standard piroxicam gel was found to inhibit arthritic edema to an extent of 66.96%. A profound anti-arthritic effect of *C.longa* curcuminoid extracts inhibit nuclear factor - kB (NF-kB) activation in rheumatoid arthritis rats, blocking multiple downstream signaling pathways critical to joint inflammation, including cyclo-oxygenase (COX) stimulated prostaglandin-E_2 (PGE_2) production (Funk*et al*., 2010).

1.7 Antidiabetic activity

C. neilgherrensis antidiabetic activity as effective drug at the minimum dose levels of 250 mg/kg b.wt. of rhizome extracts as safe drug and no toxicity and there is no negative effects on body weights and behavioural aspects; without alteration of haematological and biochemical parameters equal to that of normal rats and the standard drug glibenclamide treated rats due to the presence of high quantities of phenols and flavonoid compounds like quercitin, cyanidin, hirsutin, petunidin, malvidin, and n-heptane, α-thujene compounds. *C.neilgherrensis* rhizome may acts as potent drug in controlling the lipid peroxidation which regulates diabetic effect (Chaithra and Yasodamma, 2016). *C. neilgherrensis* is more effective than the *A. galanga* antidiabetic activity at 400 mg/kg b.wt.; *C. longa* + *Abromine angusta* at 300 mg/kg b.wt. *C. raktakanta* at 224.22 µg/ml and 961.54 µg/ml; *C. xanthorrhiza*+*Gauzuma ulmifolia* at 12.5 and 25 mg/kg b.wt., respectively (Adnyana *et al*., 2013). In *C. angustifolia* shows the presence of thujene, pipene, caryophyllene, amorphene and humulene 6-7 epoxide compounds (Nayak*et al*., 2014). Rhizomeethanolic extracts of *C. raktakantha*also revealed the presence of ethyl p-methoxycinnamate, α-pinene, β-pinene, camphor, terpinyl acetate tumerone and some oleoresins. The anti-diabetic and anti-hyperlipidemic activity shown by ECR might be due to the presence of polyphenols (Dan *et al*., 2002). Effects of *C. longa* on postprandial plasma glucose and insulin due to curcumin which inhibits nuclear factor-kappa B (NF-κB) activation and protein carbonyl, lipid peroxidation, and lysosomal enzyme.The STZ induced diabetic rats showed significant increase in fasting blood glucose and decrease in body weight. The weight loss is due to increased muscle wasting and polyuria (Habibuddin *et al*., 2008).

2. Conclusion

Phytonanotechnology is a vital tool to advance more in our understanding of plant species fundamentally and modulate plant functional activities. In present paper, we have focused majorly on species, uses and applications of various phytoconstituents for diverse pharmacological and biological activities. *Curcuma* species are important medicinal plants with several lead molecules. Hence, isolation and identification of those important molecules are needed for opening of new window in therapeutics. Beneficial effects of turmeric are traditionally achieved through dietary consumption. An effective dose, safety and mechanism of action are required for the rational use of turmeric in the treatment of human diseases. *Curcuma* species has revealed a large number of compounds, including curcumin, volatile oil and curcuminoids, turmerones which have been found to have potent pharmacological properties. The curcumin has multiple pharmacologic effects, but due to poor bioavailability therapeutic effects got suppressed which upon conjugating curcumin to metal oxide nanoparticles or encapsulation in lipid nanoparticles, dendrimers, nanogels and polymeric nanoparticles, thereby the water solubility or the bioavailability gets enhanced leading to increase its pharmacological properties. Similarly, further studies recommended for the other *Curcuma* species for different biological activities which includes anti-bacterial, antifungal, antiulcer, antidiarrhoeal, anti-inflammatory, antiarthritic, antioxidant and antidiabetic activities *etc*.

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Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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