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Novel Terpenoids as Potential Bioactive Agents Reported from Turmeric (*Curcuma longa* L.) and Black Turmeric (*Curcuma caesia* Roxb.)

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Abstract

The terpenoids have been prized for their human uses over two thousand years. Plants have the potentiality to produce a diverse nature of secondary metabolites that have versatile biological functions. Most of the phytochemicals are useful to us. About 140 different sesquiterpenes have been isolated from the genus *Curcuma*, and they can be classified into ten distinctly different structural types. However, most of these compounds fall into one of the three major categories, bisabolane, germacrane, or guaiane types. These plants used commonly in food technology as well as pharmaceutical industries. The key constituents of exhibit a wide range of bioactive potentialities like anticandiadal, antibacterial and antimetastatic activities. *Curcuma caesia* is endemic to the North East Asia, where an infusion of the rhizomatous parts of the plant is used in folk medicine as an antidiabetic, anticancerous agent. Consequently, the reveal of medicinal properties of the secondary metabolites of this plant have been the subject of an ongoing study. Now a day, solving the mystery of bioactive potentiality of natural product is one of the largest thrust areas of research in life science. Nature possesses all the disease curing agents (bioactive phytochemicals) that we need to reveal for our healthy life style. The use of Black Turmeric, Turmeric etc. in Indian tradition is found from ancient time, even when people do not exactly know the actual bioactive potentiality or mode of action of phytochemicals present in the extract of Black Turmeric and Turmeric.

Keywords: Novel Terpenoids; Bioactive Agents; Black Turmeric; Turmeric

Introduction

An archaeological investigation in Egypt in 1997 unearthed Boswellic acids from the resin of frankincense (*Boswellia sp*.) dating from 400 to 700 AD. The terpenes have a simple unifying feature by which they are defined and by which they may be easily classified. This generality, referred to as the isoprene rule or fundamental repeating five carbon units. Like all natural products, within this simple classification lies an enormous amount of structural diversity that leads to a wide variety of terpene like (or terpenoid) compounds. Some 30,000 terpenes were identified thus far. In this thesis the compound 2, 7, (14), 10 bisabolatriene- 1,9,12 triol [1] isolated from *Curcuma longa* L. is a bisabolane type sesquiterpene. Though the compound was reported from *Curcuma xanthorrhiza* Roxb. but its presence in turmeric has been reported first in the laboratory and has been included in this review. The bisabolanes are one of the three fairly

large groups of sesquiterpenes found in the genus *Curcuma*. At least 34 different bisabolane type sesquiterpenes have been reported from nine species of the *Curcuma. C. aromatica* Salisb., *C. longa* L., *C. Xanthorrhiza* Roxb., *and C. zedoaria* (Christm.) Roscoe are the four major sources of these compounds. Ar-Turmerone is the most widely distributed bisabolane type sesquiterpene within *C. zedoaria* (Christm.) *Roscoe. Bisacumol, α-curcumene, β-curcumene, and zingiberene* were reported from four or more species. While compounds α-curcumene and β-curcumene are fairly common, γ-curcumene was only isolated from *C. caesia* Roxb. [2]. *Xanthorrhizol isolated from C. aromatica Salisb. and C. xanthorrhiza* Roxb. [3], is one of the most important biologically active components of this genus.

Several other ethno medicinally important plants belonging to the genus *Curcuma* are *C. aeruginosa, C. alismatifolia, C. amada, C. angustifolia, C. aromatic, C. caulina, C. chuanyujin, C. cochinchinensis, C. comosa, C. heyneana, C. harmandii, C. kwangsiensis, C. parviflora, C. petiolata, C. phaeocaulis, C. rotunda, C. wenyujin, C. zedoaria* all of which are more or less therapeutically important. *C. aeruginosa* contains Aerugidiol, Cineole, Camphor, Curcumenol, Curdione, Curzerenone, Dehydrocurdione, Difurocumenone, Isocurcumenol, Pinene, Zedoalactone and Zedoarondio,l etc. [4]. *C. alismatifolia* contains Malvidin 3-rutino*side* [5]. *C. amada* contains Bis-demethoxycurcumin, Curcumin, Calarene, Caryophyllene, Copaene, Curzerenone, Myrcene and Terpinen-4-ol, etc. [6,7]. *C. angustifolia* contains Curzerene in its rhizome. C. aromatic is one of the wild species of *Curcuma* that possess Curcumin, Demethoxycurcumin, Acetoxyneocurdione, Acetoxydehydrocurdione, Bisabolene, Bisacumol, Carene, Carvacrol, Curzerene, etc. [7].

Curzerene, Demethoxycurcumin, 1-Feruloyloxy-2-methoxycinnamic acid, 4-Epi-curcumenol, Isocurcumenol, (E) Acetoxy-diphenyl 1 heptene, (E) Diphenyl 1 hepten 5 one, (E)- Dihydroxyphenyl -hydroxy-phenyl-heptene, Curcumanolide, Labdadiene, Oxycurcumenol, Gweicurculactone etc. have ben already reported from *C. caulina, C. chuanyujin, C. cochinchinensis, C. comosa, C. heyneana, C. harmandii, C. harmandii, C. kwangsiensis, C. xanthorrhiza, C. zedoaria,* etc [8]. The rhizomes of *C. longa* exclusively contain Cyclocurcumin, Atlantone, Calebin, Caffeic acid, Caryophyllene, Curlone, Eugenol, Farnesene, Germacrone, Procurcumadiol, Isoprocurcumenol, Sabinene, Syringic acid, Terpenolene, Terpinen, Vanillic acid, Zedoarondiol and Ukonans, neutral polysaccharides [9].

As per literature survey it is evident that few reports are available regarding the phytochemical constituents of *C. caesia*. Borneol, Bornyl acetate, Cineole, Camphor, Curcumene, Elemene, Ocimene and Turmerone have been reported till now from *C. caesia* [2,7,10]. To add some more knowledge on the phytochemical constituents of *C. caesia* we have isolated, purified and indentified more three novel phychemicals and also cited their bioactive potentialities in this thesis. These three terpenoids are C_{24}, C_{11} and C_{19} terpenoids and these are (2Z,2'Z)-2,2'- (3aR,10aS)- 1,3,5,8,9,9-hexamethyl- 1,2,3,3 a- tetrahydrobenzo [f] azulene-4,10 (5H,8H,9H,10aH)-diylidene) diacetaldehyde, (Z)-7-methoxy-1,5-dihydrobenzo[c] oxepine and 2,3,4,8a,9,9a-hexamethyl-2,3,3a,4,4a,5,8,8a,9,9a-decahydro-1H-cyclopenta [b] naphthalene-1,2,3a,4a-tetraol respectively. Al these three terpenoids isolated from *Curcuma caesia* Roxb. was reported for the first time in the field of phytochemistry.

Turmeric powder is a powerful antioxidant good for cardiovascular, skeletal, and digestive systems. It has beneficial effect on the ligaments, treatment of cervical cancer, biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis [11]. Turmeric extract possesses anti-inflammatory, anti HIV, antibacterial, antioxidant properties, and nematocidal activities [12-15]. It also has immune-enhancing properties [13,16].

In a recent study, it was suggested that most of the beneficial effects of turmeric could be related to its prominent free radical scavenging property [17]. Extracts of turmeric reduced secretion of acid from the stomach and protected against injuries such as inflammation along the stomach or intestinal walls, and ulcers caused from certain medications, stress, or alcohol. There has been a substantial amount of research on turmeric's anticancer potential against various forms of cancers including colorectal, prostate, oral, blood, and breast cancers [18]. Several authors [19] reported that turmeric extract was effective in inducing apoptosis in human myeloid leukemia cells (HL-60). Several authors studied the pharmacodynamics and pharmacokinetic behavior of oral administration of turmeric extract in patients with colorectal cancer.

The, double-ended chelating compounds, synthesized by the acetylation of diamines, have previously been reported to be very effective for cancer chemotherapy, due to their chelating effect with the substrate [20,21]. In our report also the acetylated derivative of 2, 7, (14), 10 Bisabolatriene- 1,9,12 triol shows greater antitumor activity than the parental compound [1].

Although, the crystal structure studies of many of these compounds have previously been reported [22,23] and in some cases these compounds have been used in the synthesis of their metal complexes [24-28] but no systematic studies for the characterization of these compounds have been carried out and no report on the antibacterial and antifungal studies of these compounds exists.

Turmeric also possesses antioxidant property, and this property has been implicated to its various pharmacological activities [18,29-32].

The antimicrobial activities of an ethanolic extract were evaluated against several strains of bacteria and fungi [33-36]. The extract was effective against fungi *Fusarium oxysporium, Aspergillus niger, A. nidulans, Alternaria solani, Botrytis cineria, Erysiphe graminis, Phytophthora infestans, Puccinia recondita, Pyricularia oryzae, Rhizoctonia solani* [37] and bacteria *Staphylococcus albus, Escherichia coli,* and *Pseudomonas pyocyanea, Helicobacter pylori* [38], *Actinomycetes* [18] etc.

In continuation to this there are several reports that deals with the bioactive potentialities of the pure compound isolated from different species of *Curcuma*. Curcumin, demethoxycurcumin, bis-demethoxycurcumin, and ar-turmerone possess a variety of therapeutic properties including anti alzheimer's, anticancer, antiarthritic, anti-inflammatory, antiedemic, antitumor, antimutagenic, anticoagulant, hepatoprotective, antihypercholesterolemic, nephrotonic, antihypertensive, chemoprotective, carminative, depurative, anti-HIV, antimicrobial, and antiparasitic properties [11,19]. They found to block the production of certain prostaglandins and had effects similar to cortisone and nonsteroidal anti-inflammatory drugs but without any side effects [39,40]. 5′-methoxycurcumin, from *C. xanthorrhiza* also possesses potent antioxidant activity [41].

Labda-8 (17), 12-diene- 15, 16-dial isolated from *C. longa* shows strong antifungal activity against *Candida albicans* at 1 µg/ml, and inhibited the growth of *C. kruseii* and *C. parapsilosis* at 25 µg/ml. The antibacterial potentiality of Xanthorrhizol from *C. xanthorrhiza* against *Streptococcus mutans* was also reported.

Most of the ethno medicinally important plants grow naturally in its specific season. So, the bioactive natural products present there in are not available in nature throughout the year. The solution of this problem lies within the *in-vitro* propagations of these plants. The aspects for *in-vitro* propagation do not only involve with the availability of these plants, but also with scientific conservation to maintain the biodiversity. *In-vitro* propagation also indirectly deals with the *in-vitro* production such bioactive natural products from aseptic cultures of these ethno medicinally important plants.

Improvement in tissue culture technique for the production of bioactive natural products (therapeutic compounds) has made possible the production of a wide variety of pharmaceuticals like alkaloids, terpenoids, steroids, saponins, phenolics, flavanoids, and amino acids. Mainly higher plants are the major sources of bioactive natural products used as pharmaceuticals, agrochemicals, flavor and fragrance ingredients, food additives, and pesticides [42]. Generally, the concentration of bioactive natural products in plant cell is sometimes less which may not enough to cure any disease. So, to increase the generation or production of the bioactive natural products plant tissue culture is advantageous [43]. Cell suspension culture systems is one of this advancement in tissue culture that could be used for large scale culturing of plant cells from which secondary metabolites could be easily extracted. The rationale behind choosing this system is that it can ultimately provide a continuous and reliable source of natural products [44,45].

The presence of valuable chemicals in plants stimulates interest on the part of industries in the fields of pharmaceuticals (as drug sources), agrochemicals (for the supply of natural fungicides and insecticides, crop protactant), nutrition (for the acquisition of natural substances used for flavoring and coloring foods), and cosmetics (natural fragrances). The world market for biotechnological products increased greatly in recent decades. For example, in 2000, biopharmaceuticals represented a global market valued at over $12 billion (U.S. currency). Since then, the industry has expanded considerably, despite being severely limited by the manufacturing capacity and cost of the production systems currently in place. Therefore, an alternative source for desired secondary metabolites is of great interest. Cell and tissue cultured plant materials can be an attractive alternative as a production system and as a model system with which to study the regulation of natural product biosynthesis in plants to ultimately increase yields.

Thus, plant biotechnology can supply information to optimize phytochemical production in plant cell and tissue culture through sustainable, economically viable cultivation. However, trials with different plant cell cultures initially failed to produce high levels of the desired products. Several medicinal plants are employed in our studies concerning plant cell biotechnology. These include Hawthorn (*Crataegus*), which produces proanthocyanidins and several kinds of flavonoids used for the treatment of heart disease; St. John's wort (*Hypericum perforatum*), which produces anti-depressant and anticancer compounds like hyperforin and hypericins; Flax (*Linum spp.*), for the production of cytotoxic lignans such as podophylotoxin and 5 methoxy podophylotoxin; Kudzu (*Pueraria montana*) as a source of isoflavones, daidzein, genistein, and their respective glucoside conjugates, daidzin (daidzein 7 O glucoside) and genistin (glucosyl 7 genistein) plus puerarin (daidzein 8 C glucoside). Each of these plants made important contributions to the pharmaceutical industry. In all plant cell studies, the up regulation of biosynthesis processes of

several compounds using genetic and epigenetic approaches are now being considered as viable approaches. A new direction of research in plant cell biotechnology, namely, plant metabolic engineering, is currently progressing rapidly. Rational engineering of secondary metabolic pathways requires a thorough understanding of the whole biosynthetic pathway and an unraveling of the regulatory mechanisms. Recent achievements were made in the altering of various pathways by use of specific genes encoding biosynthetic enzymes or genes that encode regulatory proteins [46,47]. In addition, new antisense genes are used to block competitive pathways. This could increase the total flux toward the desired secondary metabolites [48]. Shifting attention from recombinant proteins to metabolic engineering introduces new challenges. A better understanding of the basic metabolic process could be key information needed to produce high-value natural products.

There is another important factor concerning the accumulation and storage of desired secondary metabolites in plants. Secondary metabolites in cell and tissue cultures are usually stored intracellular, as for example, in vacuoles or multicellular cavities, and transporters probably play an important role in the sequestration of secondary metabolites [49]. Moreover, many biosynthetic pathways in plants are long and complicated, requiring multiple enzymatic steps to produce the desired end-product. The major aims for engineering secondary metabolism in plant cells are to increase the content of desired secondary compounds, to lower the levels of undesirable compounds, or to introduce novel compound production into specific plants. Plant metabolism, however, concerns thousands of interacting pathways and processes. Therefore, engineering even known metabolic pathways will not provide the expected results. Extensive metabolic profiling must be more systematic and involve considerable analysis in this case. Productive metabolic engineering, therefore, is based on a systems biology approach involving integrated metabolomics, proteomics, and transcriptomics approaches [50,51]. Despite major advances in metabolic engineering, only a few secondary metabolic pathways were enzymatically characterized and the corresponding genes cloned. In this context, the biosynthetic pathways for alkaloids, flavonoids, and terpenoids are presently the best characterized at the enzyme and gene levels. Metabolic engineering is a potentially powerful tool for the regulation of secondary metabolism in transgenic plants, and it will certainly have many applications in the future [48].

The active principle content (bioactive natural products or therapeutic compounds) varies from organ to organ of the plant. Callus induction in tissue culture regime yield undifferentiated mass of cells results in homogenous production of active principle content throughout the culture. This innovation indirectly also leads to increase in massive *in-vitro* production of active principles.

Another possible way to increase the *in-vitro* production of active principles by Bio-transformations [52-55]. In this system, desired genes responsible for production of desired phytochemicals are transferred and expressed in *in-vitro* culture so that enhancement in the production of specific photochemical can be achieved. Due to these advances, research in the area of tissue culture technology for production of plant chemicals has bloomed beyond expectations [56]. Transgenic hairy root cultures have revolutionized the role of plant tissue culture in secondary metabolite production [57-61]. The various kinds of biotransformation processes are summarized in the following Table 1 along with their advantages and disadvantages.

Biotransformation processes	Advantages	Disadvantages
Agrobacterium mediated	Very effective, cheap and simple to use. Also can be used in germ line transformation.	Requires the use of a tissue culture regeneration procedure. Host range may be limited by the plant hypersensitive response.
Electroporation	Very effective for transient expression. Diverse host range. High DNA delivery rate.	Also requires the use of a tissue culture regeneration procedure. Copy number of DNA insertions can be high and sometimes resulting in gene silencing through co-suppression.
Particle bombardment	Very effective especially for transient expression. No problems regarding host range.	Also requires the use of a tissue culture regeneration procedure. Copy number of DNA insertions can be high and sometimes resulting in gene silencing through co-suppression.

Table 1: Comparison of different biotransformation processes.

Conclusion

In conclusion we can say that *in-vitro* culture of ethno medicinally important plants for production of selective bioactive principles is found to be highly useful for commercial production of the medicinally important compounds. This large scale production in industries do not solely depends upon modern *in-vitro* culture techniques, but also with an improved understanding of the secondary metabolic pathways. This combined technology of *in-vitro* culture and improved knowledge regarding secondary metabolic pathways provide new means for the cost effective, commercial production of even rare or exotic plants, their cells, and the key phytochemicals that they will produce. Substantial progress in improving secondary metabolite production through *in-vitro* cultures has already been made within last few years, and with a progressive continuation to this, this field will lead to controllable and successful biotechnological production of specific, valuable, and as yet unknown plant phytochemicals in recent future.

So, there is a lot of work to be done in the field of phytochemistry, evaluation of their bioactive potentialities and application of plant biotechnology to improve the yield of phytochemicals including scientific conservation of these valuable ethno medicinally important plants. In our thesis, some steps have been attempted to enrich the information regarding the research of phytochemistry, evaluation of their bioactive potentialities and scientific conservation of few ethno-medicinally important plants (*Curcuma longa L*. and *Curcuma caesia* Roxb.).

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Conflict of Interest

There are no conflict of interest in this work.

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