ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Aspergillus Mediated Biotransformation: A Review

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ABSTRACT

In the resurgence of natural compound discovery, fungi contribution is marked significant. However, the traditional isolation of bioactive compounds has led to yield disappointment. Thus targeted application of biotransformation resolves this problem; by harnessing the enzyme with the microorganism to produce the useful compound in bulk quantity drives its attention of several pharmaceutical, food and agrochemical industries. In this review we discuss about different classes of compounds involved in biotransformation producing myriad of lead molecules catalysed by different species of *Aspergillus*.

Keywords: *Aspergillus,* Biotransformation, Terpenoids, Steroids, Flavonoids.

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ISSN: 0975-8585

INTRODUCTION

Microorganisms have the potential to produce diverse secondary metabolites with wide range of bioactivity which drives the attention of several pharmaceutical, food and agrochemical industries [1]. Microbial secondary metabolites originate from few biosynthetic pathways, which undergo enzyme-catalysed reaction to produce diverse array of chemical molecules. Thus these secondary metabolites are classified based on their biosynthetic origin as terpenoids, flavonoids, steroids, polyketids, alkaloids, amino acids etc., Last few decades witnessed the decline in search of new molecules of pharmaceutical industry interest [2]. Natural products produced from microorganisms, gains advantage over synthetic in showing greater structural diversity. Thus resurgence of natural product discovery is in progress and fungi make a significant contribution to it [3].The genus *Aspergillus* has the tremendous capacity to produce myriad bioactive compounds. The pathogens are gaining resistance to several antibiotics, pesticides has created the major threat to pharmaceutical and agricultural industries. Thus there is an urgent need to combat multidrug resistant pathogen and unlocks the natures treasure for new leads. However, the traditional isolation of bioactive compounds has led to yield disappointment. Thus targeted application of biotransformation resolves this problem [4].The technology which harnesses the enzyme with the microorganism to produce the useful compound in bulk quantity drives its attention. The use of micro organisms in the synthesis of antibiotics, steroids, flavonoids, amino acids and polysaccharides in large scale industrial production has grown to larger phase in recent times. Thus biotransformation is the recognition of two streams of science i.e., microbiology and organic chemistry. Microbial transformation makes use of enzyme catalysed reaction like oxidation reduction, hydrolysis, degradation and formation of regio and sterio specific bonds. Some advantages in selecting microbial reaction over chemical synthesis is they functionalise specific position in the molecule, sterio and regio specific substitutions are made easy, microbial reactions are mild hence maintain the stability of the molecule, cost effective, optical resolutions of racemic mixtures are made easy. Hence microbial biotransformation has markedly increased the ability of industrial production (chemical and pharmaceutical industries) of new biocatalyst. In this review we discuss about biotransformation of terpenoids, steroids and flavonoids with the aid of well known fungus *Aspergillus*.

Biotransformation of Terpenoids

Terpenoids (**Fig. 1**) are large class of organic compounds produced from plants and by some insects. They are formed by combination of several isoprenoid units.

Monoterpenoids: Monoterpenes are widely distributed in nature and find extensively in flavour and fragrance industry [5]. It consist of only two isoprene units and may be linear (acyclic) or contain rings. Monoterpenoids are metabolized by fungi [6, 7]. *A. niger* ATCC 9142 transforms Cinerone (**Fig. 1A**), to cinerolone by hydroxylation at the 4-position, cinerolone an intermediate in the synthesis of insecticides [8]. (−)Menthol (**Fig. 1B**), a monoterpenoid flavoring compound from peppermint, is also used as a local anesthetic is biotransformed with a strain of *A. niger* to produce the 1-, 2-, 6-, 7-, 8-, and 9-hydroxymenthols [9].The cyclic ether 1,4-cineole from lime juice is transformed by *A. niger* UI 172 to (±)-2-exo-hydroxy-1,4-cineole, a key precursor in herbicide synthesis, and (±)-2-oxo-1,4-cineole [10]. Karahanaenone, derived from the hop plant, is transformed to a mint aroma compound, (S)-karahanaenol, by a strain of *A. niger* (Miyazawa et al 1995). (+)-Limonene, a cyclic monoterpene is metabolized by *A. niger* strain to perillyl alcoho and organic acids [11]. Geranyl acetate (**Fig. 1C**) is metabolized by *A. niger* geraniol and 8- hydroxygeraniol, with 50% and 40% yield, respectively [12]. Geranylacetol is converted by a strain of *A. niger* to 11-hydroxygeranylacetol and 9,10-dihydroxygeranylacetol, whereas geranylacetone is converted to (*S*)- (+)-geranylacetol, 11-hydroxygeranylacetone, and (*S*)-(−)-9,10-dihydroxygeranylacetone, some of which are useful for the synthesis of optically active compounds [13].The mycelium of *A. niger* LCP 521 hydrolyzes geranyl N-phenylcarbamate to form (6*R*)-geranyl N-phenylcarbamate diol with an enantiomeric excess over 95% [14].

Sesquiterpenoids: Three isoprene units are used to make up the sesquiterpenoids, many of which have anti-inflammatory and other medicinal properties. α-Santalene (**Fig. 1D**) a fragrant sesquiterpene from sandal wood essential oil, is metabolized by a strain of *A. niger*, to teresantalic acid which is used as a flavoring ingredient [15]. Costunolide (**Fig. 1E**), a sesquiterpenoid lactone from magnolia trees that is cytotoxic to tumor cells in vitro, is converted by *A. niger* ATCC 16888 to dihydrocostunolide ,colartin, 11,13-dihydrosantamarine, 11,13-dihydroreynosin , and tetrahydrovulgarin [16]. Farnesol (**Fig. 1F**), a sesquiterpenoid alcohol from plant essential oils, is used in perfumes, tobacco flavouring, and pesticides. A mixture of farnesol isomers is

hydroxylated by *A. niger* DSM63263 to produce 12-hydroxyfarnesol [17]. (+)-Germacrone-4,5-epoxide , a epoxide derived from a species of turmeric, is transformed by a strain of *A. niger* into zedoarondiol and isozedoarondiol [18]. Curdione (**Fig. 1G**) , from a traditional Chinese medicine, is transformed by growing cells of *A. niger* as 3.739 to several metabolites, including 3 α-hydroxycurdione, 2 β-hydroxycurdione,curcumalactone,3α-hydroxycurcumalactone,(10*S*)-9,10 dihydroxycurcumalactone, and (10R)-9,10-dihydroxy-curcuma-lactone [19]. A sesquiterpenoid ketone, 1,4,4-trimethyltricyclo(5.4.0.03,5) undec-7-en-9-one, is hydroxylated at the 13- and 12-methyl groups by *A. niger* ATCC 9142 to produce 4(*S*)- and 4(*R*)-(hydroxymethyl)-1,4-dimethyltricyclo(5.4.0.03,5) undec-7- en-9-one, respectively [20]. Drimenol (**Fig. 1H**) , a sesquiterpenoid alcohol from the Winter's bark tree of Chile and Argentina, is useful for chiral synthesis. Hydroxylation by a strain of *A. niger* produces 3 β-hydroxy-(−)-drimenol; drimenyl acetate is also transformed to the corresponding 3 β-hydroxy derivative [21]. Sclareolide (**Fig. 1I**) , a sesquiterpenoid lactone used as a fragrance, is transformed by *A. niger* ATCC 10549 to five metabolites: 3-ketosclareolide, 1 β and 3 β-hydroxysclareolide, and 1α,3 β- and 1 β,3 β-dihydroxysclareolide [22]. The important antimalarial drug artemisinin (**Fig. 1J**) is trans-formed by *A. niger* AS 3.795 to 4 β-hydroxy deoxyartemisinin , yield 15% in 4 days [23]. Another strain, *A. niger* AS 3.1858, transforms artemisin into 4 α-hydroxydeoxyartemisinin , yield 26%) and 5a- α-hydroxy deoxyartemisinin (yield 13%) in 3 days [24]. *A. niger* VKM F-1119 hydroxy-lates artemisinin to 5 β-hydroxy artemisinin (yield 80%) and 7 β-hydroxyartemisinin, (yield 19%) [25]. A sesquiterpenoid cyclic ether from a liverwort, (−)-maalioxide, is hydroxylated by a strain of *A. niger* to three metabolites: 1 β-hydroxy-(−)-maalioxide, 1 β,9 β-dihydroxy-(−)-maalioxide and 1 β,12-dihydroxy-(−)-maalioxide [26].

Diterpenoids: Diterpenoid found in plant resins consist of two terpene units in a variety of arrangements. They are not used as fragrances, but several of them have medicinal properties, especially the taxoids produced by yew trees, which have valuable anti-cancer activity.17-Norkauran-16-one and ent-17-norkauran-16-one, which are tetracyclic diterpenoids that are possible gibberellin precursors in plants, are biotransformed by *A. niger* ATCC26693 to the 3 β-hydroxy and 3 α-hydroxy derivatives, respectively [27]. In contrast, 17-norphyllocladan-16-one is biotransformed to the 3 β-hydroxy and the 3-keto derivatives [27]. Isosteviol (**Fig. 1K**), an ent-beyer-19-oic acid derivative with a variety of biological effects, is biotransformed by *A. niger* CMI 17454 to form 7 β-hydroxyisosteviol and 1 α,7 β-dihydroxyisosteviol [28]. Another strain, *A. niger* IFO 4414, metabolizes isosteviol not only to 7 β-hydroxyisosteviol but also to 11 β- and 12 β-hydroxyisosteviol; these metabolites have antitumor activity [29]. Isosteviol lactone is biotransformed by *A. niger* BCRC 31130 to seven different hydroxylated diterpenoids, which is targeted to inhibit the activator protein-1 transcription factor [30]. *A. niger* BCRC 32720 hydroxylated Isostevic acid to eight metabolites with anti-inflammatory properties [31]. Baccatin VI , a taxoid diterpenoid from a Chinese yew tree, can be biotransformed with *A. niger* BCRC 31130 to produce the diterpenoids taxumairol S1 and taxumairol T1 , which have been used in antitumor research [31]. Neoandrographolide , a diterpenoid from a Chinese traditional medicinal plant, is biotransformed by *A. niger* AS 3.739 to five products: 15-olid- 19-oic acid, 13-ent-labdadien-16, 19-hydroxy-8(17),13-ent-labdadien-16,15-olide, 18-hydroxy-8(17),13-ent-labdadien-16,15-olid-19-oic acid, 3 α- hydroxy-8(17),13-ent-labdadien-16,15-olid-19-oic acid, and 8 β,19-dihydroxy-ent-labd-13-en-16,15-olide [32]. Imbricatolic acid **(Fig. 1L)** a diterpenoid obtained from the common juniper, is region selectively transformed by cultures of *A.niger* ATCC 16404 to 1 α-hydroxyimbricatolic acid in 15days [33].

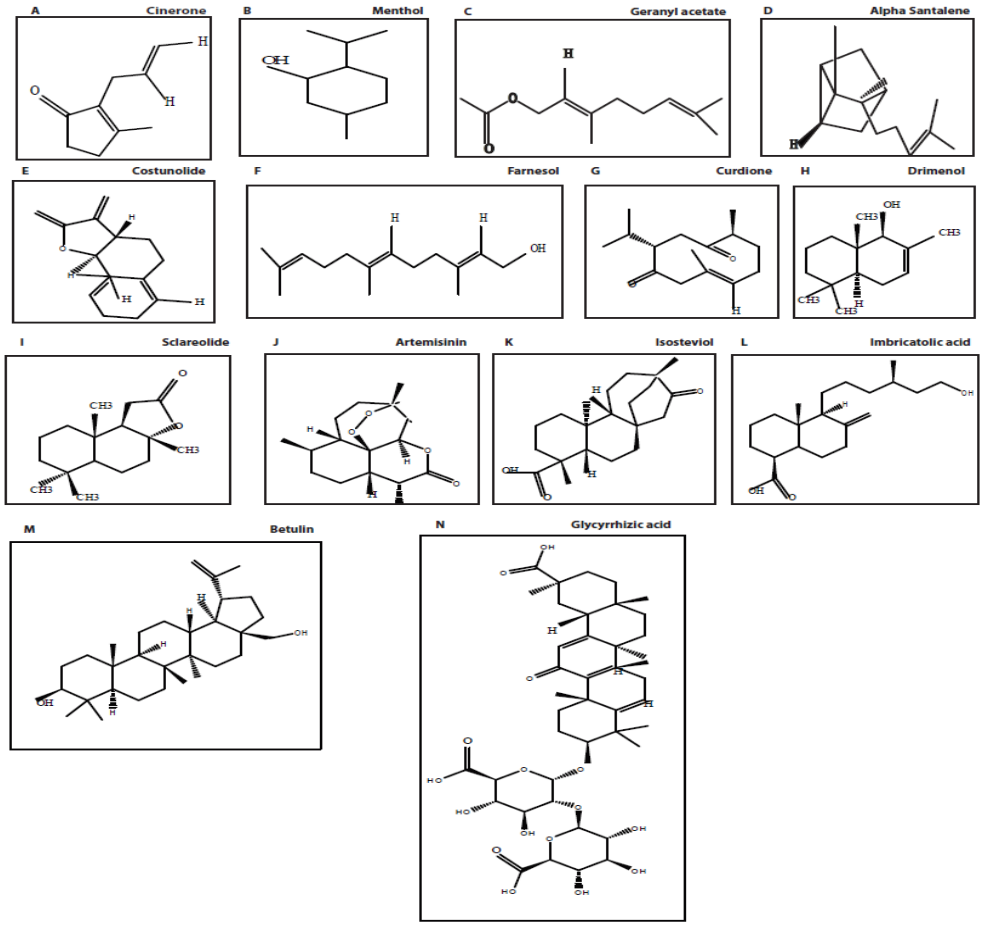
Triterpenoids: Triterpenes are a class of chemical compounds composed of three terpene units or six isoprene units. They are components of traditional medicines that are being investigated for anticancer and other pharmaceutical effects; and some are the precursors of steroids. The betulinic acid production from betulin [34], (**Fig. 1M**) is biotransformed by *A.foetidus* ZU-G1 and *A. oryzae* AS 3.498 and observed methyl group migration from C-19 to C-20 and transformation of the C-28 carboxyl group into a C-28 hydroxyl group. Platycodin D, a triterpenoid saponin with two side chains, from the root of the Asian bell flower, is transformed from *A. niger* KCTC 6906 to a saponin which lack the terminal xylose and of apiose .This derivative has greater nitrite-scavenging activity and less toxicity [35]. A triterpenoid saponin derived from licorice, glycyrrhizic acid (**Fig. 1N**), is metabolized by a strain of *A. niger* that removes two glucuronic acid residues to produce the triterpenoids 7 β,15 α-dihydroxy-3,11-dioxo-oleana-12-en-30-oic acid and 15 α- hydroxy-3,11-dione-oleana-12-en-30-oic acid [36]. Three synthetic olean-type pentacyclic triterpenes, 3-oxo oleanolic acid, 3-acetyl oleanolic acid and esculentoside A with *A. ochraceus* CICC 40330 was reported by [37]. Lupane terpenoids are a group of pentacyclic triterpenoids is known as inhibitors against glycogen phosphorylase and antimalarial, vasorelaxant activities. Pentacyclic triterpenes of the lupane type, such as lupeol, betulin and betulinic acid, is known for its bioactivities including antiviral, in particular against to human immunodeficiency

ISSN: 0975-8585

virus [38],herpes simplex virus [39] and antitumor against human melanoma and other types of human malignancies [40]. *A. ochraceus* metabolized pentacyclic triterpene lupeol to two derivatives [41].

Biotransformation of Terpenoids Fig 1(A-N):

Figure 1



Biotransformation of Steroids:

The most important non-saponifiable class of lipids are the steroids (**Fig. 2**). They are recognised by their tetracyclic skeleton, with three fused six membered and one five-membered ring and bears close resemblance to cholesterol. These compounds include bile salts, cholesterol and certain hormones produced widely by animals, partly by plants [42] and also by fungi [43]. Apart from the origin they have wide applications in therapeutics, cosmetics and nutrition.

Androstendione: Biotransformation with adrostane like compounds resulted in production of testosterone as compound, which is gaining attention in pharmaceutical application. Production of 17β-Hydroxyandrost-4-en-3-one and D-Homo-17α-oxaandrost-4-en-3, 17-dione was reported when Androstendione (**Fig. 2A**) was incubated with *A. terreus* PTCC 5283 [44].

Cholic acid: Cholic acid is considered as one of the important components of bile acids in humans. Cholic acid and its derivative are gaining much attention in pharmaceutical and therapeutic (Fig. 2B) applications [45]. Biotransformation of methyl cholate using was reported to isolated two compounds 3α, 7α, 12α, 15β-tetrahydroxy-5β-cholan- *A. niger* 3α, 12α-dihydroxy-7-oxo-5β-cholan-24-oate [46].

Testosterone: the best-known as anabolic steroids male hormone, is metabolized by *A. sydowii* MRC 200653 by hydroxylation at C-6β, C-14α and C-15α to produce 3 metabolites 6β, 17β-Dihydroxyandrost-4-en-3-one 5,

14α, 17β-Dihydroxyandrost-4-en-3-one 6, 15α, 17β-Dihydroxyandrost-4-en-3-one 7. [47]. Hydroxylation of Testosterone (**Fig. 2C**) was also reported in *A. wentii* MRC 200316 producing 6β-hydroxytestosterone and 14α-hydroxytestosterone [48]. 15 β-hydroxytestosterone was reported from *A. fumigatus* [49].

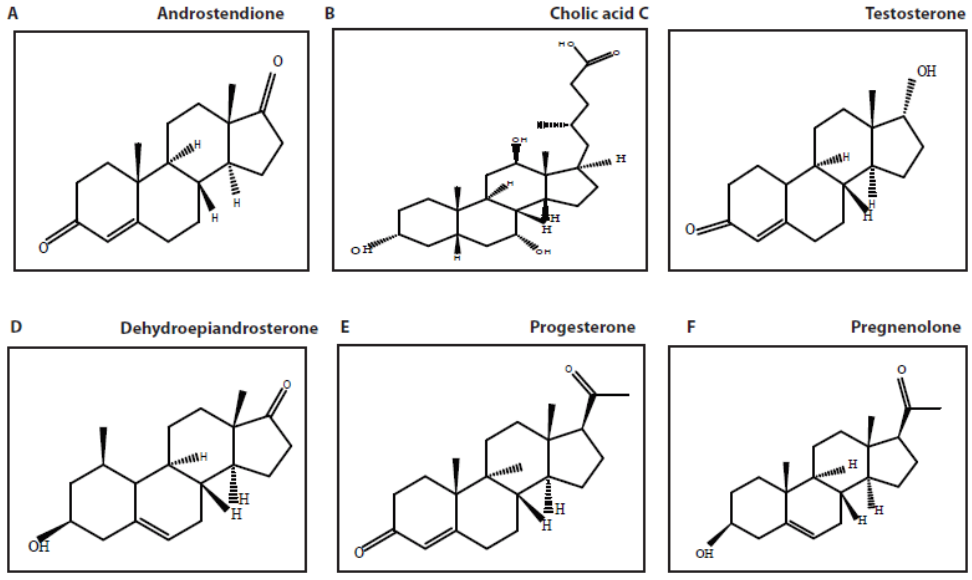
Dehydroepiandrosterone : an endogenous steroid hormone, is reported to be metabolized by *A.sydowii* MRC 200653 by hydroxylation at C-6β to produce 3 metabolites 6β-Hydroxyandrost-4-en-3,17-dione 8, 3β,7β-Dihydroxyandrost-5-en-17-one 9, 3β,7α-Dihydroxyandrost-5-en-17-one 10 [47]. *A. niger* NRRL 599, were also used to biotransform dehydroepiandrosterone (**Fig. 2D**) to 4-androstene-3,17-dione, 17 β -hydroxy- 4-androstene-3, I 6-dione, 16 β, 17 β -dihydroxy-4-androsten-3-one and a new compound, 16 β hydroxY-4-androstene-3,17-dione by16,β-hydroxylation [50].16β-hydroxylation was also observed in *A. niger* TCCC41650 to produce 16β-hydroxy-androst-4-ene-3, 17-dione upon transformation [51].

Progesterone: Progesterone (Fig. 2E) an endogenous steroid hormone, is metabolized by *A. sydowii* MRC 200653 by hydroxylation at C-11α, C-15β,C-6β and C-7β to produce 5 metabolites 15β-Hydroxypregn-4-en-3,20-dione 11, 11α-Hydroxypregn-4-en-3,20-dione 12, 11α,15β-Dihydroxypregn-4-en-3,20-dione 13, 7β,15β-Dihydroxypregn-4-en-3,20-dione 14, 6β,11α-Dihydroxypregn-4-en-3,20-dione 15 [47]. Hydroxylation of Progesterone was also reported in *A. wentii* MRC 200316 producing 11α-hydroxyprogesterone [48].

Pregnenolone: Pregnenolone (**Fig. 2F**) is an endogenous steroid and a precursor, is metabolized by *A. sydowii* MRC 200653 by hydroxylation at C-11α, C-15β,C-6β and C-7β to produce 5 metabolites 15β-Hydroxypregn-4-en-3,20-dione 11, 11α-Hydroxypregn-4-en-3,20-dione 12, 11α,15β-Dihydroxypregn-4-en-3,20-dione 13, 7β,15β-Dihydroxypregn-4-en-3,20-dione 14, 6β,11α-Dihydroxypregn-4-en-3,20-dione 15. [47].

Biotransformation of Steroids Fig 2(A-F):

Figure 2



Biotransformation of Flavonoids

Well known as antioxidant and metal-ion chelator. Ubiquitous phenolic compounds found in nature. It shows wide range of physiological and pharmaceutical applications showing antioxidant [52], antimicrobial [53], antiviral [54], antiplatelet [55], anti-inflammatory [56], antiallergic [57], antihemolytic [58], antitumor [59] etc. The structure of flavanoid (**Fig. 3**) consists of a flavan nucleus with 15 Carbon derived from C6-C3-C6 skeleton with second aromatic ring B. Flavonoids is classified into different subclasses based on the established of the functional groups attachment as Flavone, Flavonol, Flavonone, Isofalvones, Catechins, Chalcones, Flavonoids are widely produced in plants and partly by microorganisms and animals.

Flavone: Flavone (**Fig. 3A**) back bone has the characteristic double bond between C2 and C3 positions. Biotransformations of flavone by many fungi including species of *Aspergillus, Cunninghamella, Helicostylum, Linderina, Penicillium and Streptomycetes* gave 4′-hydroxy-flavone and 3′,4′-dihydroxyflavone as the major compounds. By employing *Aspergillus niger* isolated from *Allium sativum* in transformation of Flavone to isolate two metabolites and identified as 2'-hydroxydihydrochalcone and 2'-hydroxyphenylmethylketone which proved to be more potent in antimicrobial property against *P. aeruginosa, Escherichia coli, Bacillus subtilis, and Klebsiella pneumonia, Fusarium moniliforme, A. flavus, Saccharomyces cerviceae, Kluveromyces lactis and C. albicans* than flavones itself [60]. Flavone on hydroxylated to 4′-hydroxyflavone by A. niger ATCC 43949 to produce to 3′,4′-dihydroxyflavone [61]. Nobiletin (Fig. 3B) is transformed to 4′-hydroxy-5,6,7,8,3′-pentamethoxyflavone by *A. niger* IFO 4414 showing antimutagenic activity. Tangeretin (**Fig. 3C**)is demethylated to 4′-hydroxy-5,6,7,8-tetramethoxyflavone by *A. niger* ATCC 984199 and Hydroxytangeretin to 3,4′-dihydroxy- 5,6,7,8-tetramethoxyflavone by *A. niger* ATCC 9142 [62].

Flavonone: Flavonone (**Fig. 3D**) which has a characteristic one reduced double bond at C2 and C3 is metabolized to different products by several strains of *Aspergillus.* With the aid of *A. niger* KB flavanone and 6-hydroxyflavanone (**Fig. 3E**) was biotransformed to produce Flavan-4-ol and 6-hydroxyflavan-4-ol. Hydroxylation at C-5 was confirmed by A. ochraceus 456 where biotransformation of 7-hydroxyflavanone (**Fig. 3F**) was carried out to produce 5, 7-dihydroxyflavan-4-ol and in case of *A. niger* dehydrogenation of C-2 and C-3 was observed after 9 days of biotransformation of 7-hydroxyflavanone to produce 7-Hydroxyflavone [63]. Phellamurin, a flavanone glucoside is hydrolyzed to aglycone neophellamuretin by *A. niger* IAM-25[64].

Isoflavones: Isoflavones (**Fig. 3G**) are class of compounds derived from plants resembling estrogen. Recently some reports proved that some microbes can also produce flavones and isoflavones through de novo synthesis [65].Because of the structural similarity they interfere with the estrogen and compete for the same receptor sites thereby decreasing the risk of excess estrogen, and also increase estrogenic activity. Isoflavones was proved to have several biological activities which includes antifungal [66], antioxidant [67], antiinflammatory anticancer [68] etc.,

A. niger was employed in biotransformation of 7,4′-dimethoxyisoflavone (Fig. 3H) was converted to 6-hydroxy-7,4′-5 dimethoxyisoflavone by oxidation at the C-6 position and daidzein by demethylation of methoxy groups at the C-7 and C-4′ positions. 7,4′-3 diacetoxyisoflavone was converted to daidzein (**Fig. 3I**) by hydrolysis at the C-7 and C-4′ positions [69].Incubations of isoflavanone with *A. niger* X 172 led to the formation of 2-hydroxy isoflavanone and 3',4'-dihydroxyisoflavone indicated hydroxylation of C-2, C-3, or ring B. Dehydrogenation of isoflavanone to isoflavone and isoflavone to flavone was also observed by *A. niger* NRRL 599 [70]. *A. niger* NBRC 4414 was used to transform 7,4′-Dimethoxyisoflavone to daidzein and 7,4′-dimethoxy-6-hydroxyisoflavone; and 7,4′-diacetoxyisoflavone was transformed to daidzein [71].Biotransformation of some isoflavones catalysed by Aspergillus niger was also observed successful wherein 6,7,4'-trimethoxyisoflavone and S,7,4'-trimethoxyisoflavone were demethylated at the C-4' position to form 4'-hydroxy-6,7-dimethoxyisoflavone and 2 to 4'-hydroxy-5,7-dimethoxyisoflavone with regioselectivity [72]. It also proved that *A. niger* could rapidly metabolize 4'- hydroxyisoflavone to 3',4'-dihydroxyisoflavone and 3',4'-tri-hydroxyisoflavone

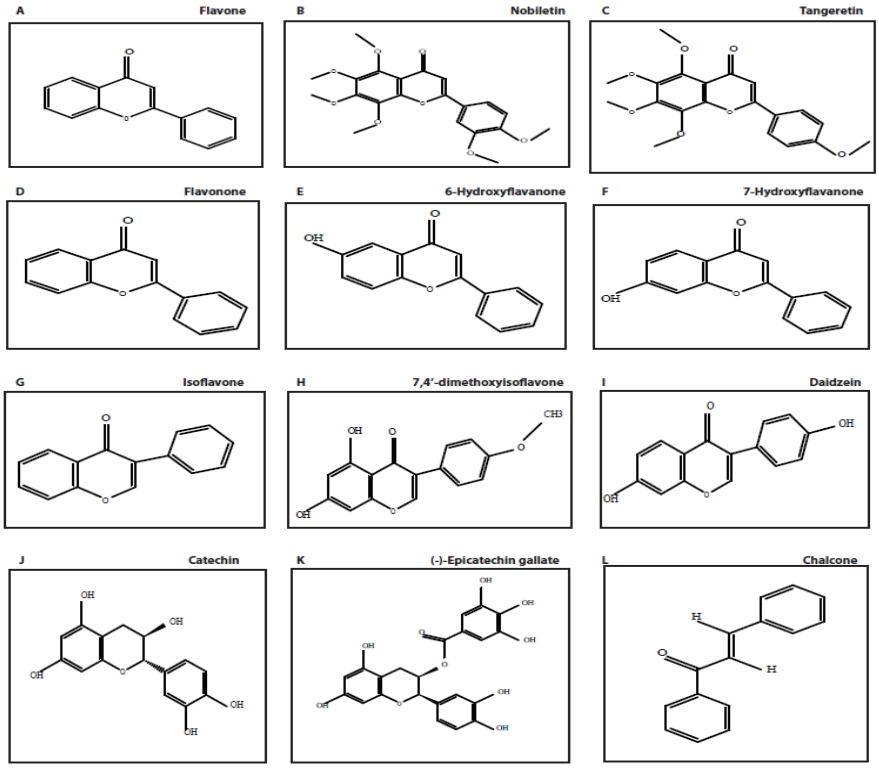
Catechins: Catechins(Fig. 3J) is a flavan-3-ol, a natural phenol and antioxidant derived from plant. Hydrolysis of (−)-epigallocatechin gallate(Fig. 3K) an ester from green tea is transformed to (−)-epigallocatechin and gallic acid by *A. oryzae* [73].

Chalcones: or Chalconoids (Fig. 3L)is an aromatic ketone and an enone are natural phenols derived from plants. It forms the central core for a variety of important biological compounds. They are important as they show antimicrobial, antitumor and anti-inflammatory properties. Endophytic fungi *A. flavus* isolated with *Paspalum maritimum* Trin plant were known to biotransform chalcone, 3,4,5-trimethoxychalcone and 2,3,4,4'-tetramethoxychalcone were biotransformed to dihydrochalcone, 3,4,5-trimethoxydihydrochalcone and 2,3,4,4'-tetramethoxydihydrochalcone respectively [74]. *A. alliaceus* UI 315 efficiently transformed 3-(2′′,3′′-dimethoxyphenyl)-1-(2′-hydroxyphenyl)propenone (2′-hydroxy-2,3-dimethoxychalcone) to 2′,3′-dimethoxyflavanone, $C_{16}H_{15}O_4$ and $C_{16}H_{15}O_5$ [75].

ISSN: 0975-8585

Biotransformation of flavonoides Fig 3(A-L):

Figure 3



CONCLUSIONS

Aspergillus species is a treasure and natural gift which is employed in exploration and exploiting its involvement from basic production of secondary metabolites to its genomic level. Thus establishing its strong platform in the area of biology and chemistry in pharmaceuticals, food and agrochemical industry. Enzyme and microorganism are versatile catalyst which is capable to transform many different groups of compounds/secondary metabolites, often with high regio and stereo selectivity. Metabolites involved in catalysis with different species of *Aspergillus* to produce sterio and regio modified compounds is shown in table 1. Metabolites produced in high yield may have value for use as experimental drugs or in further organic synthesis, while the metabolites produced in minute quantity cannot be brought further for clinical trials. Thus biotransformation simplifies the problem by synthesizing the natural compounds in bulk with the aid of microorganisms is receiving a key interest in the field of enzyme technology and organic chemistry. The most useful biotransformation should be acquiescent to improved methods and scale up so that larger quantities of new metabolites may be made available for investigation.

Table 1: Various products formed after catalysis of substrate with the *Aspergillus*

Substrate/Compound	*Aspergillus* species	Product
Terpenoids		
Cinerone	*A. niger* ATCC 9142	Cinerolone
(−)Menthol	*A. niger*	1-hydroxymenthol
		2-hydroxymenthol
		6-hydroxymenthol
		7-hydroxymenthol
		8-hydroxymenthol
		9-hydroxymenthol
1,4-cineole	*A. niger* UI 172	(±)-2-exo-hydroxy-1,4-cineole
		(±)-2-oxo-1,4-cineole
Karahanaenone	*A. niger*	(S)-karahanaenol

(+)-Limonene	*A. niger*	perillyl alcoho
Geranyl acetate	*A. niger*	geraniol
		8- hydroxygeraniol
Geranylacetol	*A. niger*	11-hydroxygeranylacetol
		9,10-dihydroxygeranylacetol
Geranylacetone	*A. niger*	(S)- (+)-geranylacetol
		11-hydroxygeranylacetone
		(S)-(−)-9,10-dihydroxygeranylacetone
Geranyl N-phenylcarbamate	*A. niger* LCP 521	(6R)-geranyl N-phenylcarbamate diol
Costunolide	*A. niger* ATCC 16888	dihydrocostunolide
		colartin
		11,13-dihydrosantamarine
		11,13-dihydroreynosin
		tetrahydrovulgarin
Farnesol	*A. niger* DSM63263	12-hydroxyfarnesol
.(+)-Germacrone-4,5-epoxide	*A. niger*	zedoarondiol
		isozedoarondiol
Curdione	*A. niger* AS 3.739	3 α-hydroxycurdione
		2 β-hydroxycurdione
		curcumalactone
		3α-hydroxycurcumalactone
		(10S)-9,10 dihydroxycurcumalactone
		(10R)-9,10-dihydroxy-curcuma-lactone
1,4,4-trimethyltricyclo(5.4.0.03,5) undec-7-en-9-one	*A. niger* ATCC 9142	4(S)-(hydroxymethyl)-1,4-dimethyltricyclo(5.4.0.03,5) undec-7- en-9-one
		4(R)-(hydroxymethyl)-1,4-dimethyltricyclo(5.4.0.03,5) undec-7- en-9-one
Drimenol	*A. niger*	3 β-hydroxy-(−)-drimenol
Sclareolide	*A. niger* ATCC 10549	3-ketosclareolide
		1 β- hydroxysclareolide
		3 β- hydroxysclareolide
		1α,3 β-dihydroxysclareolide
		1 β,3 β-dihydroxysclareolide
Artemisinin	*A. niger* AS 3.795	4 β-hydroxydeoxyartemisinin
Artemisin	*A. niger* AS 3.1858	4 α-hydroxydeoxyartemisinin
		5a- α-hydroxydeoxyartemisinin
Artemisinin	*A. niger* VKM F-1119	5 β-hydroxy artemisinin
		7 β-hydroxyartemisinin
(−)-Maalioxide	*A. niger*	1 β-hydroxy-(−)-maalioxide
		1 β,9 β-dihydroxy-(−)-maalioxide
		1 β,12-dihydroxy-(−)-maalioxide
17-Norkauran-16-one	*A. niger* ATCC26693	3 β-hydroxy derivatives
Isosteviol	*A. niger* CMI 17454	7 β-hydroxyisosteviol
		1 α,7 β-dihydroxyisosteviol
Isosteviol	*A. niger* IFO 4414	7 β-hydroxyisosteviol
		11 β- hydroxyisosteviol
		12 β-hydroxyisosteviol
Baccatin VI	*A. niger* BCRC 31130	taxumairol S1
		taxumairol T1
Neoandrographolide	*A. niger* AS 3.739	15-olid- 19-oic acid
		13-ent-labdadien-16
		19-hydroxy-8(17),13-ent-labdadien-16,15-olide
		18-hydroxy-8(17),13-ent-labdadien-16,15-olid-19-oic acid
		3 α- hydroxy-8(17),13-ent-labdadien-16,15-olid-19-oic acid
		8 β,19-dihydroxy-ent-labd-13-en-16,15-olide
Imbricatolic acid	*A.niger* ATCC 16404	1 α-hydroxyimbricatolic acid
Betulin	*A.foetidus* ZU-G1	betulinic acid
Betulin	*A. oryzae* AS 3.498	betulinic acid

Platycodin D	*A. niger* KCTC 6906	saponin
Glycyrrhizic acid	*A. niger*	7 β,15 α-dihydroxy-3,11-dioxo-oleana-12-en-30-oic acid
		15 α- hydroxy-3,11-dione-oleana-12-en-30-oic acid
Steroids		
Androstendione	*A. terreus* PTCC	17β-Hydroxyandrost-4-en-3-one
		D-Homo-17α-oxaandrost-4-en-3
		17-dione
Methyl cholate	*Aspergillus niger*	3α,12α-dihydroxy-7-oxo-5β-cholan-24-oate
Testosterone	*A. sydowii* MRC 200653	6β, 17β-Dihydroxyandrost-4-en-3-one 5
		14α, 17β-Dihydroxyandrost-4-en-3-one 6
		15α, 17β-Dihydroxyandrost-4-en-3-one 7
Testosterone	*A. wentii* MRC 200316	6β-hydroxytestosterone
		14α-hydroxytestosterone
Dehydroepiandrosterone	*A.sydowii* MRC 200653	6β-Hydroxyandrost-4-en-3,17-dione 8
		3β,7β-Dihydroxyandrost-5-en-17-one 9
		3β,7α-Dihydroxyandrost-5-en-17-one 10
Dehydroepiandrosterone	*A. niger* NRRL 599	4-androstene-3,17-dione
		17 β -hydroxy- 4-androstene-3, I 6-dione
		16 β, 17 β -dihydroxy-4-androsten-3-one
		16 β hydroxY-4-androstene-3,17-dione
Progesterone	*A. sydowii* MRC 200653	15β-Hydroxypregn-4-en-3,20-dione 11
		11α-Hydroxypregn-4-en-3,20-dione 12
		11α,15β-Dihydroxypregn-4-en-3,20-dione 13
		7β,15β-Dihydroxypregn-4-en-3,20-dione 14
		6β,11α-Dihydroxypregn-4-en-3,20-dione 15
Progesterone	*A. wentii* MRC 200316	11α-hydroxyprogesterone
Pregnenolone	*A. sydowii* MRC 200653	15β-Hydroxypregn-4-en-3,20-dione 11
		11α-Hydroxypregn-4-en-3,20-dione 12
		11α,15β-Dihydroxypregn-4-en-3,20-dione 13
		7β,15β-Dihydroxypregn-4-en-3,20-dione 14
		6β,11α-Dihydroxypregn-4-en-3,20-dione 15
Flavonoides		
Flavone	*A. niger* ATCC 43949	3’,4’-dihydroxyflavone
Nobiletin	*A. niger* IFO 4414	4’-hydroxy-5,6,7,8,3’-pentamethoxyflavone
Tangeretin	*A. niger* ATCC 984199	4’-hydroxy-5,6,7,8-tetramethoxyflavone
Hydroxytangeretin	*A. niger* ATCC 9142	3,4’-dihydroxy- 5,6,7,8-tetramethoxyflavone
Flavonone	*A. niger* KB	Flavan-4-ol
6-hydroxyflavanone	*A. niger* KB	6-hydroxyflavan-4-ol
7-hydroxyflavanone	*A. ochraceus* 456	5, 7-dihydroxyflavan-4-ol
7-hydroxyflavanone	*A. niger*	7-Hydroxyflavone
7,4’-dimethoxyisoflavone	*A. niger*	6-hydroxy-7,4’-5 dimethoxyisoflavone
		daidzein
Isoflavanone	*A.niger* X 172	2-hydroxy isoflavanone
		3',4'-dihydroxyisoflavone
Isoflavanone	*A. niger* NRRL 599	isoflavone
Isoflavone	*A. niger* NRRL 599	flavone
7,4’-Dimethoxyisoflavone	*A. niger* NBRC 4414	daidzein
		7,4’-dimethoxy-6-hydroxyisoflavone
(−)-Epigallocatechin gallate	*A. oryzae*	(−)-epigallocatechin
		gallic acid
3-(2’’,3’’-dimethoxyphenyl)-1-(2’-hydroxyphenyl)propenone (2’-hydroxy-2,3-dimethoxychalcone)	*A. alliaceus* UI 315	2’,3’- dimethoxyflavanone

ACKNOWLEDGEMENT

We would like to thank Department of Science and Technology, India for the DST Inspire fellowship (GAP-0347). We thank Dr. Ramars Amanchy for suggestions and critical review of the manuscript.

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