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Biotransformation of natural compounds by fungal microorganisms and their biological activities

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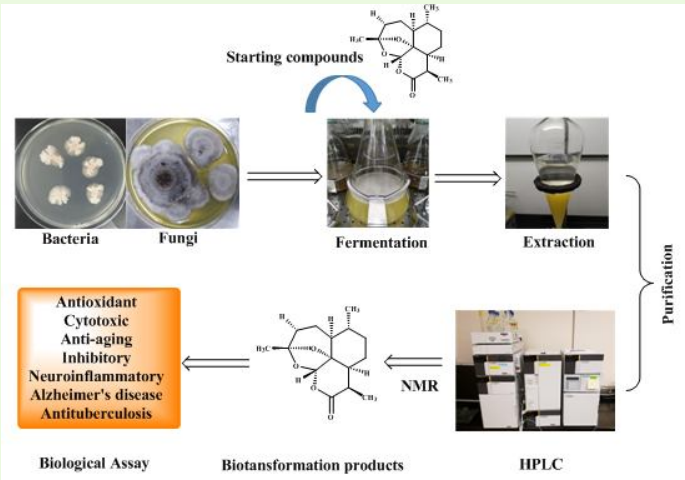
Abstract

Biotransformation of natural compounds involves the modification of bioactive molecules by bacteria and fungi, resulting in derivatives that are more potent, stable, or bioavailable. This process plays a crucial role in drug discovery, particularly in pharmaceuticals and medicinal chemistry. Whole-cell biotransformation utilizes microorganisms to convert natural compounds into bioactive derivatives. Enzymes from these microorganisms catalyze key reactions such as oxidation, hydrolysis, and methylation, enhancing the stability, potency, and bioavailability of the resulting compounds. This review provides a comprehensive summary of 116 modified metabolites produced through microbial transformation by various microorganisms. We explore their chemical structures and pharmacological properties, highlighting their significance. This review aims to support researchers in biotechnology, organic chemistry, medicinal chemistry, and pharmacology by offering valuable insights into these biotransformation products.



1. Introduction

Microorganisms associated with natural sources play a vital role in ecosystems and are found in various environments such as water, soil, animals, plants, and biological systems. They are essential for maintaining ecological balance and facilitating numerous bio-geochemical processes (Rustamova *et al.,* 2024; Litao *et al.,* 2023). Microorganisms in these systems interact dynamically, contributing to the stability and health of ecosystems, while also playing a key role in various industrial and biotechnological applications. Microbial transformation, especially through fungal microorganisms, is a sophisticated process that broadens the variety and functional potential of natural compounds (Anas *et al.,* 2022). Microbial modification holds significant potential for generating a wide variety of structurally diverse organic compounds, particularly complex natural products such as triterpenoids, steroids, alkaloids, flavonoids, and others (Phurailatpam *et al.,* 2022; Rustamova *et al.,* 2022). These processes are valuable for creating semi-synthetic analogues and novel lead molecules (Telrandhe and Gunde, 2022). The biotrans-

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formation of natural products is recognized as an efficient strategy for discovering novel derivatives with unique properties (Thomas *et al.,* 2022; Kumar *et al*., 2022). Additionally, it provides a precise method for conducting regio and stereoselective reactions under mild and controlled conditions (Srinivasan and Murali, 2022). Biotransformation is a valuable tool for phytochemists seeking new compounds resulting from various reactions, including oxidation, reduction, hydrolysis, carbon-carbon bond formation, addition and elimination, glycosidic transfer, halogenation, and dehalogenation of natural and synthetic compounds.

In the past decade, the microbial modification of natural compounds derived from various plants by fungal microorganisms has emerged as an expanding area of research in phytochemistry. This includes the isolation, analysis, structural diversity, biological properties, biosynthetic pathways, and pharmacological applications of the resulting biotransformation products. In this review, we summarize a search conducted in the Scopus (www.scopus.com) and Web of Science (www.webofknowledge.com) databases from January 2020 to December 2024, using the keywords "biotransformation", "microbial transformation", "fungal microorganisms" and "biotransformation products". The search focused on research studies that explored the phytochemical and pharmacological aspects of microbial modification of natural compounds by fungal microorganisms found in plants, soil, water, and other environments. This summary presents 116 biotransformation products modified by fungal microorganisms, along with their taxonomy (Figure 1), and discusses their biological properties.

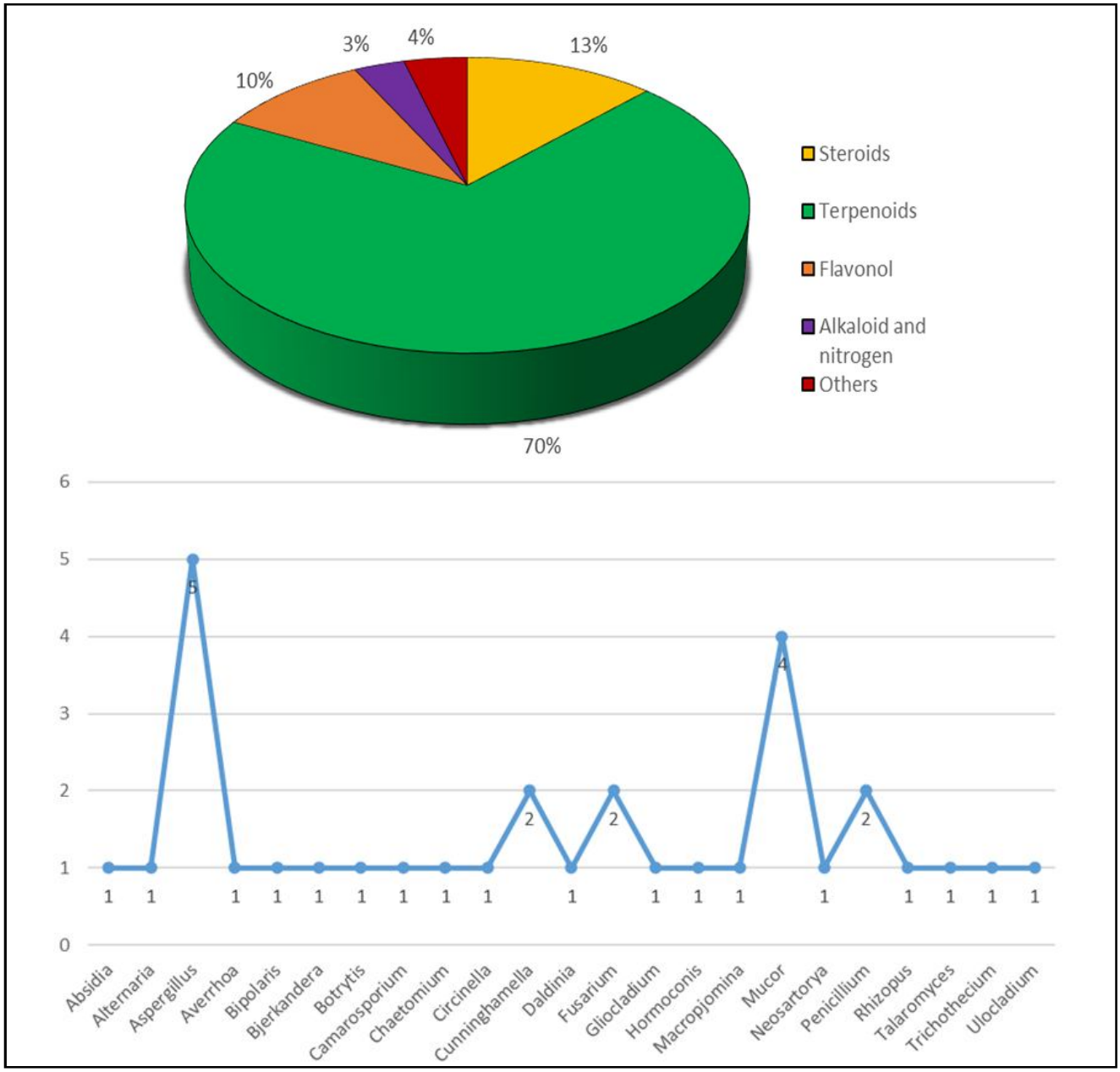
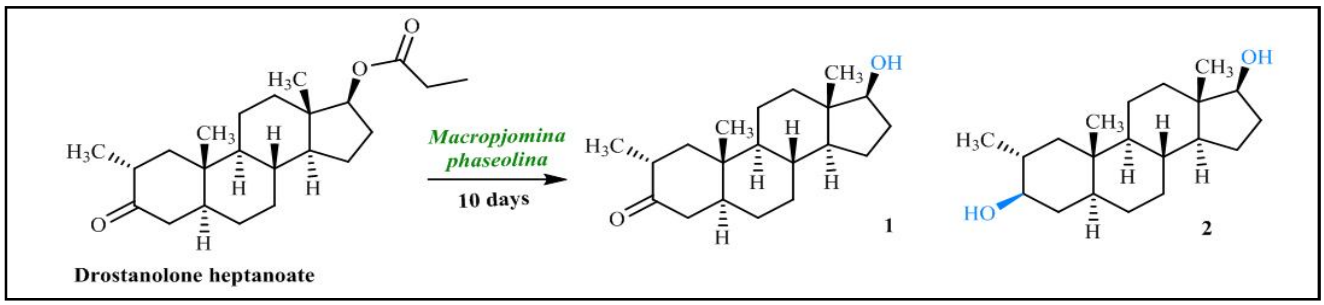


Figure 1: Biotransformation products modified by fungal microorganisms and their taxonomy.

1.1 Steroids

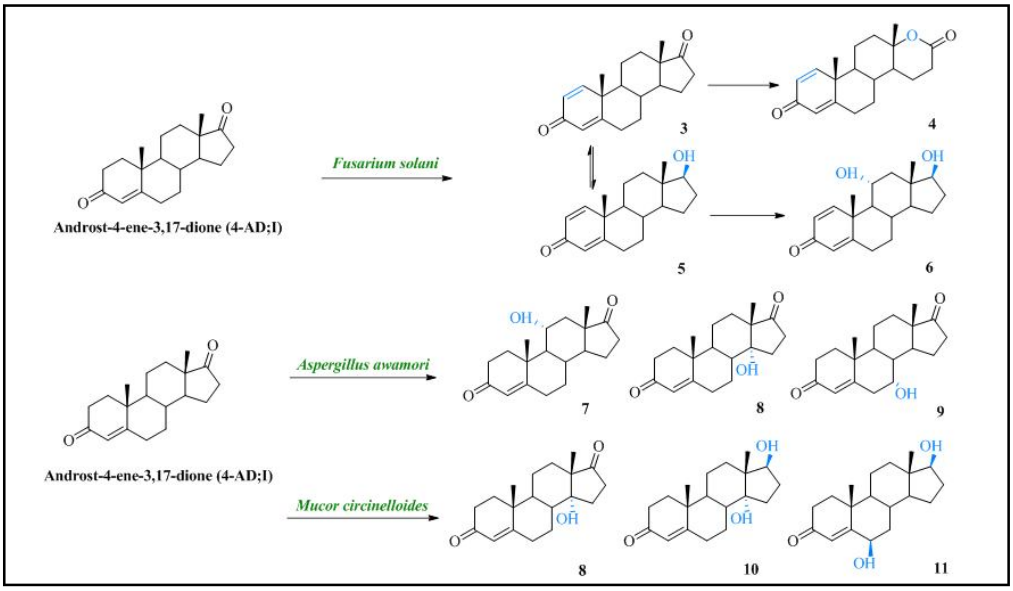
Steroids are a distinct group of bioactive natural compounds characterized by a four-ring core structure, commonly found in animals, plants, and microorganisms. In particular, the majority of steroids have been isolated from various medicinal plants, including *Cistus ladanifer, Cistus monspeliensis, Erica arborea, Globularia alypum, Pistacia lentiscus,* and *Rhamnus alaternus.* Moreover, steroids have been investigated for their antimicrobial, anticancer, anti-inflammatory, antioxidant, and antidiabetic properties (Albano *et al.,* 2021). Endophytic fungi and bacteria can enhance the bioactivity and bioavailability of steroids by modifying them through hydroxylation, oxidation, and glycosylation. This biotransformation process holds great potential for drug development and metabolic engineering.

Two different fungal strain selected for microbial modification such as *Macropjomina phaseolina*. The fungal strain collected from the American Type Culture Collection and Karachi University Culture Collection. Formation procedure carried out GPY medium (50 g/l glucose, 25 g/l peptone, and 25 g/l yeast extract, 25 g/l KH_2PO_4, 25 g/l NaCl, and 50 ml/l glycerol). Two biotransformation as 2α-methyl-17β-hydroxy-5α-androstan-3-one (1), and 2α methyl-3β,17β-dihydroxy-5α-androstane (2, Scheme 1) were isolated (Hussain *et al.,* 2020).



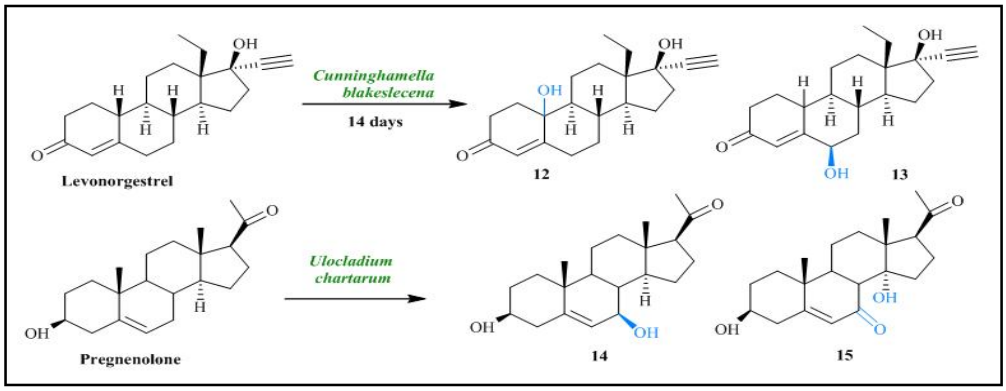
Scheme 1: The structure of the drostanolone heptanoate 1 and 2 biotransformation product produced by the endophytic fungus with *M. phaseolina*.

Three fungal strains were isolated from soil and used for biotransformation as bio biocatalysts. During of biotransformation process fungi were incubated in the liquid medium (peptone (1.2%), dextrose (3.0%), KH_2PO_4 (0.09%), yeast extract (0.1%) and distilled water with pH 4.5.). Starting compound androst-4-ene-3,17-dione (4-AD;I) was modified by fungi, formed ten novel transformation products. *Fusarium solani* BH1031 modified of initial compound androst-4-ene-3,17-dione (4-AD;I) to androst-1, 4-diene-3, 17-dione (3), which was then transformed to 17α-oxa-D-homo-androst-1, 4-diene-3, 17-dione (5) through Baeyer-Villiger oxidation. An equilibrium between products ADD (3) and 1-dehydrotestosterone (4) observed on account of the reversible redox reaction at 17-C carbonyl group by 17b-HSD. For 1 dehydrotestosterone (4), hydroxylation at position of C-11a produced 11a,17b dihydroxyandrost-1,4-diene-3-one (6) (Scheme 2). Fungus *Aspergillus awamori* MH18 was produced three biotransformation products as 11α-hydroxyandrost-4-ene-3, 17-dione (7),14α-hydroxyandrost-4-ene-3, 17-dione (8) and 7α-hydroxyandrost-4-ene-3, 17-dione (9). *Mucor circinelloides* W12 also produced three metabolites: 14α-hydroxyandrost-4-ene-3, 17-dione (8),14α, 17β-dihydroxyandrost-4-ene-3-one (10), 6β, 17β-dihydroxyandrost-4-ene-3-one (11) (An *et al.,* 2021).

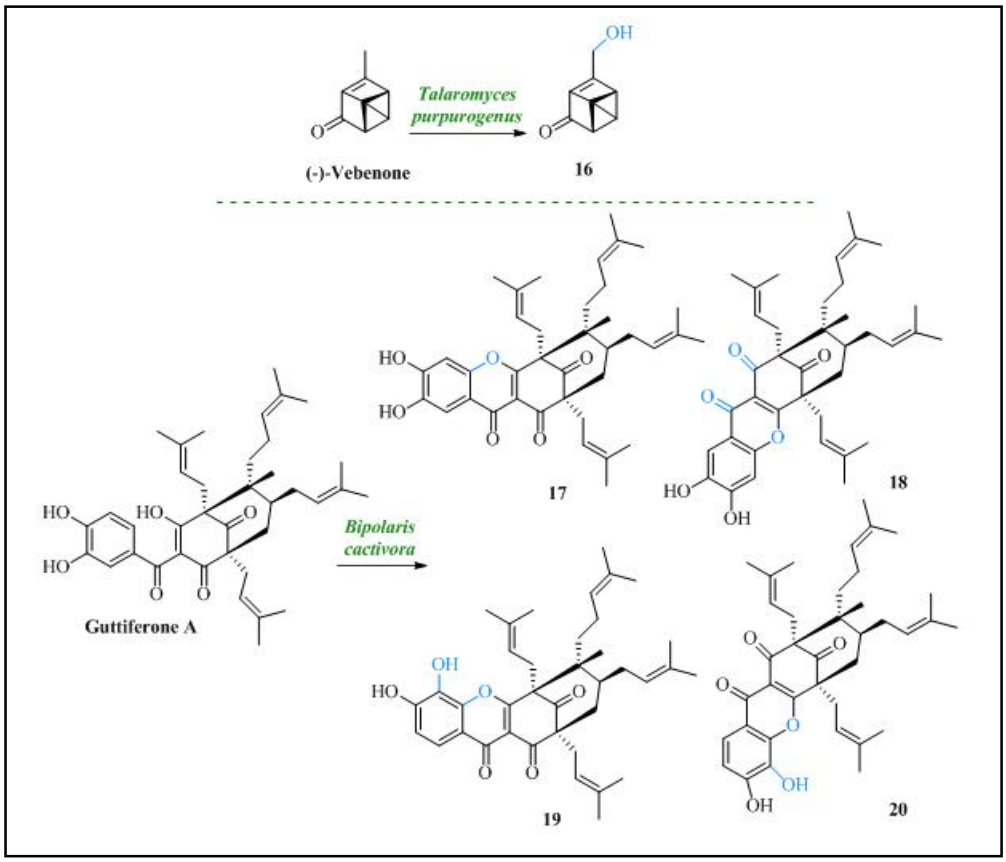


Scheme 2: The structure of the androst-4-ene-3,17-dione (4-AD; I) 3-11, biotransformation product produced by the endophytic fungi with *F. solani* BH1031, *A. awamori* MH18 and *M. circinelloides* W12.

Levonorgestrel, a highly effective contraceptive, exhibits both stimulatory and inhibitory effects on breast cancer cells. Despite lacking direct binding affinity for the estrogen receptor (ER), it exerts potent estrogen-like activity *in vitro* (Santillán *et al.,* 2001). Currently, the fungal strain catalyzed biotransformation of levonorgestrel in the presence of *C. blakesleeana* for two weeks, produced two transformation product, as (13α-ethyl-17α-ethynyl-10β,17β-dihydroxy-4-en-3-one), (12), and (13β-ethyl-17α-ethynyl-6β,17β-dihydroxy-4-en-3-one) (13) (Scheme 3) as dehydrogenation and hydroxylation reactions occurred (Kudaibergenova *et al.,* 2021). Pregnenolone is a naturally occurring neurosteroid and obtained various sources, including the mycelial cultures of *Fomitiporia aethiopica*, *Fusarium oxysporum* SC1301, *Trichoderma citrinoviride* , and the roots of *Holarrhena curtisii*. Notably, pregnenolone and its derivatives can also be synthesized through organic chemistry. This compound has demonstrated several biological activities, including cytotoxic effects and the inhibition of CYP17α hydroxylase (Al-Masoudi *et al.,* 2016). The suspension cell culture of *Ulocladium chartarum* MRC 72584 can bio-converte pregnenolone into 3β,7β-dihydroxypregn-5-en-20-one (14) (Scheme 3) and 3β,14α-dihydroxypregn-5-en-7,20-dione (15) (Kuru and Yildirim, 2022).



Scheme 3: The structure of the levonorgestrel (12-13) and pregnenolone (14, 15) biotransformation product produced by the endophytic fungi with *C. blakeslecena* and *U. chartarum*.



Scheme 4: The structure of the (-)-vebenone (16) and guttiferone A (17-20) biotransformation product produced by the endophytic fungi with *T. purpurogenus* and *B. cactivora.*

1.2 Terpenoids

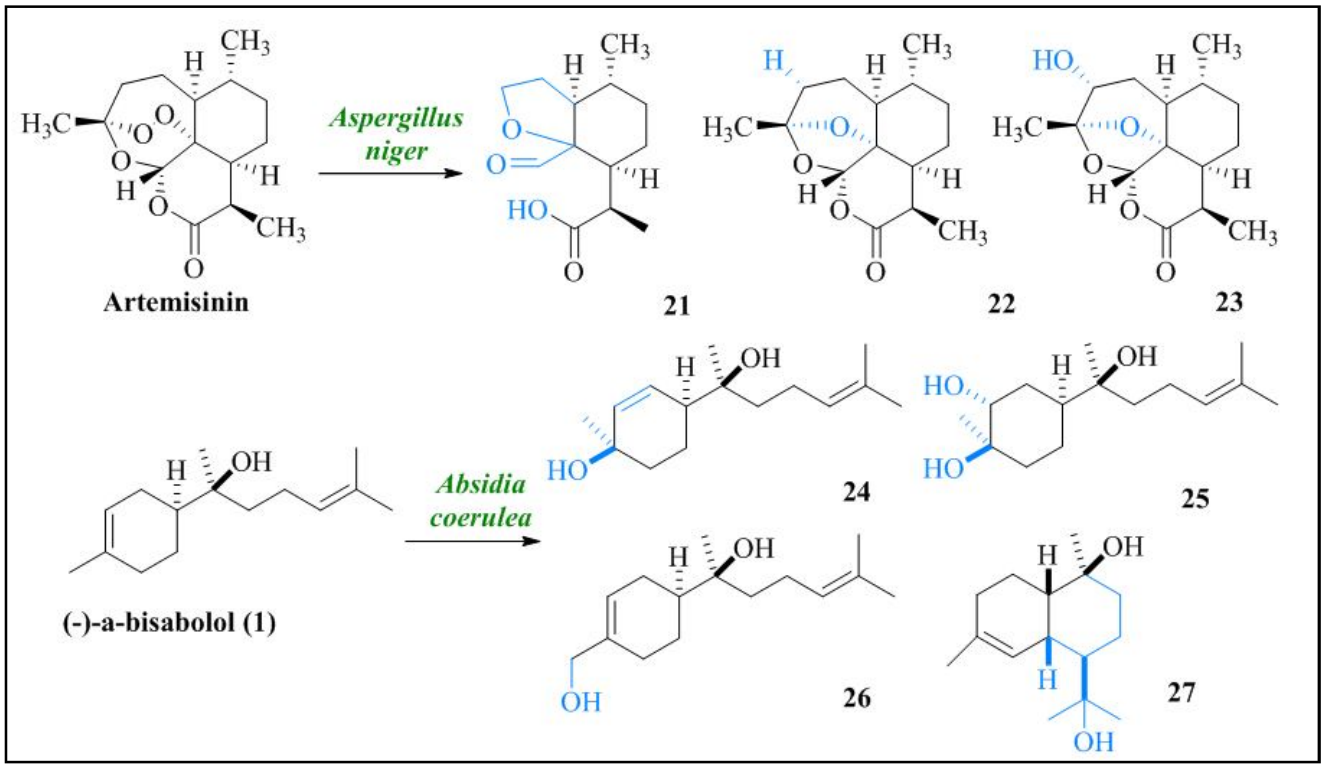
Terpenes and terpenoids represent the largest class of secondary metabolites found in plants and microorganisms. Terpenoids attract significant attention in the pharmaceutical and medicinal chemistry due to their bioactive properties. Researchers are particularly focused on their potential antimicrobial, anticancer, anti-inflammatory, and antioxidant effects (Câmara *et al.,* 2024). Terpenoids are responsible for the fragrance, flavor, and color characteristics of plants. Their classification is determined by the number of carbon atoms derived from the isoprene units they contain. For example: monoterpene, sesquiterpene, diterpene, triterpene and tetraterpene.

1.3 Monoterpene

The natural monoterpene verbenone was incubated with the fungal strain *Talaromyces purpurogenus* MRS-F13 in a fermentation broth, resulting in its conversion to (-)-10-hydroxyverbenone (16) (Scheme 4) (Manhas *et al.,* 2024). Investigations into the anti-inflammatory activity revealed that (-)-verbenone and its biotransformed product moderately inhibited TNF-α and nitric oxide, while (-)-10-hydroxyverbenone exhibited enhanced antioxidant activity. Guttiferone A was microbially transformed by the fungal strain *Bipolaris cactivora*, yielding four biotransformation products: 3,16-oxyguttiferone A (17), 1,16-oxyguttiferone A (18), 3,12-oxyguttiferone A (19), and 1,12-oxyguttiferone A (20) (Scheme 4) (Menelle *et al.,* 2021).

1.4 Sesquiterpene

The *stereo*- and *region*- specific microbial transformation of artemisinin by endophytic fungus *A. niger* yielded three metabolites including metabolite (21), deoxyartemisinin (22) and 3-hydroxy-deoxyartemisinin (23) (Scheme 5) (Luo *et al.,* 2022). (-)-a-bisabolol is insoluble in water lipophilic compound was modified by fungal microorganisms *Absidia coerulea* yielded four biotransformation products; namely, (1S,7S)-4,7-dihydroxy-α-bisabolol (24), (1S,3R,4R,7S)-3,4-dihydroxy-α-bisabolol (25, Scheme 5), 15-hydroxy-α-bisabolol (26) and 11-hydroxy-Tmuurolol (27) (Park, *et al*., 2022).



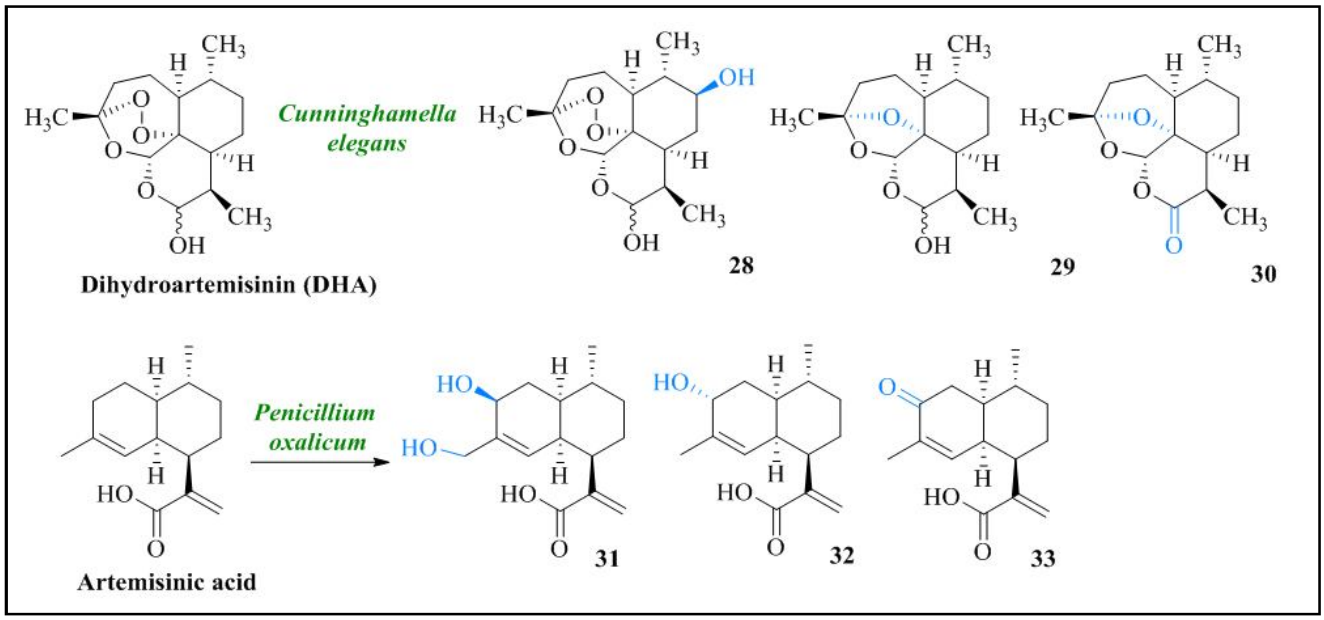
Scheme 5: The structure of the artemisinin (21-23) and (-)-a-bisabolol (24-27) biotransformation product produced by the endophytic fungu with *A. elegans* and *A. coerulea*.

Artemisinic acid and its derivatives have been identified in various species of the *Artemisia* genus, such as *A. vulgaris*, *A. annua*, *A. austriaca*, *A. absinthium*, and *A. pontica* (Trifan *et al.,* 2022). This bioactive compound is particularly significant for its potent antimalarial properties and has been widely utilized in traditional medicine systems, including those of China and India [52]. Beyond its antimalarial effects, artemisinic acid also exhibits anticancer, antioxidant, and antimycobacterial activities. Additionally, various derivatives of artemisinic acid have been synthesized and explored for their biological effects (Kotammagari *et al.,* 2020). One notable derivative, dihydroartemisinin, is a bioactive compound derived from artemisinin and primarily sourced from *A. annua.* It plays a crucial role in malaria treatment within traditional Chinese medicine. Furthermore, dihydroartemisinin has been reported to possess anti-inflammatory, anticancer, and anti-malignancy properties, highlighting its therapeutic potential (Singh and Lai 2001).

Dihydroartemisinin (DHA), a sesquiterpene lactone and a semi-synthetic derivative of artemisinin, is derived from the sweet wormwood plant (*A. annua*). It exhibits a wide range of biological activities, including antimalarial, antimicrobial, anticancer, anti-inflammatory, and immunomodulatory effects (Zhou *et al.,* 2024).

The biotransformation of DHA involves the use of fungal microorganisms to modify DHA into novel derivatives. This approach has the potential to produce compounds with enhanced pharmacological properties or unique bioactivities. Bai *et al.* (2022), reported the microbial modification of dihydroartemisinin using the fungal strain *Cunninghamella elegans* CICC 40250, resulting in the production of three modified compounds: 7β-hydroxydihydro-artemisinin (28, Scheme 6), 1-deoxydihydroartemisinin (29), and 1-deoxyartemisinin (30). Moreover, Compound 28 exhibited significant antimalarial activity, with an IC_{50} value of 133 nM against *P. falciparum* (Pf.) 3D7.

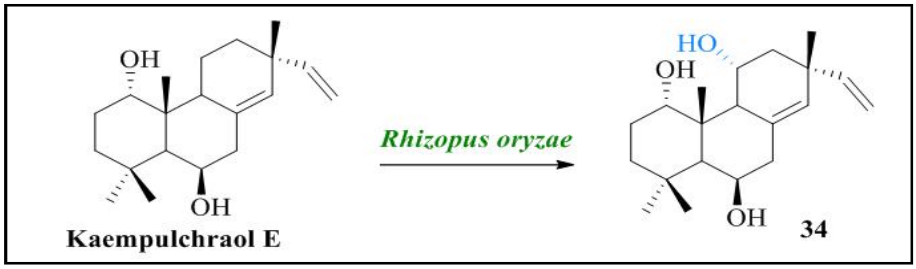
The antimalarial drug artemisinic acid were transformed into three hydroxylated biotransformation products (31), 3-α-hydroxyartemisinic acid (32), and 3-β-hydroxyartemisinic acid (33, Scheme 6) using the endophytic fungus *P. oxalicum* B4. All compounds were assessed for their cytotoxic activity against RAW 264.7 human cancer cell lines, compounds 7 demonstrated non-dose-dependent cytotoxicity against RAW 264.7 cells. Compound 7 may have potential for development as an anti-inflammatory agent (Tian *et al.,* 2021).



Scheme 6: The structure of the dihydroartemisinin (28-30) and artemisinic acid (31-33) biotransformation product produced by the endophytic fungi with *C. elegans* and *P. oxalicum*.

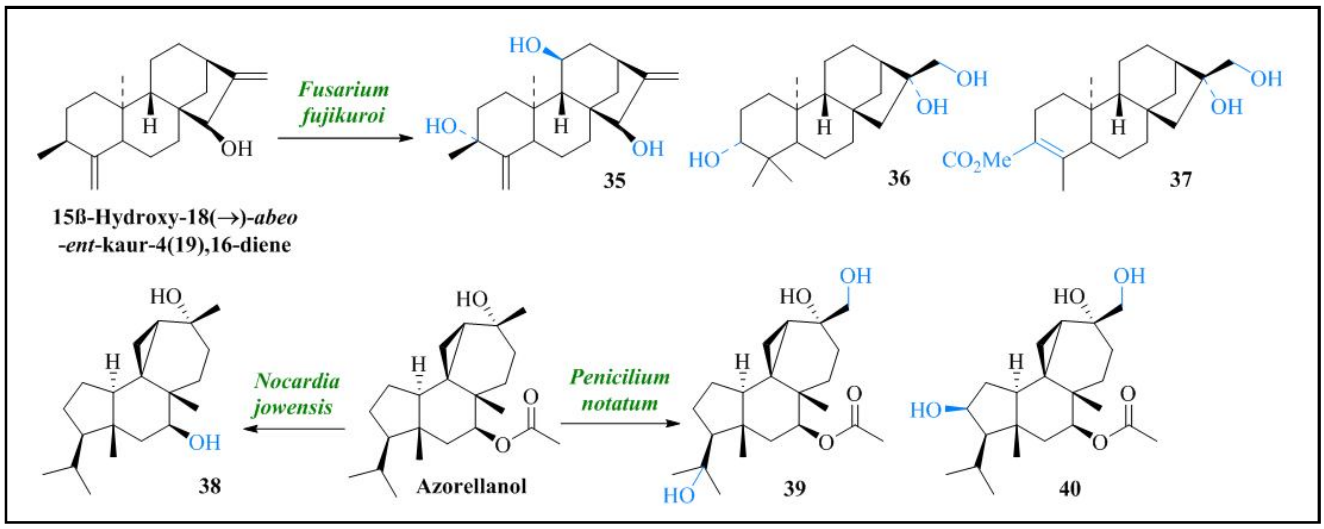
1.5 Diterpenoid

Kaempulchraol E is a natural compound commonly recognized as a chalcone derivative or a type of flavonoid. It has been extracted from several plant species, with a notable presence in members of the Zingiberaceae family, particularly the *K. pulchra, K. takensis*. Kaempulchraol E and its related compounds hold significant value in pharmaceutical research due to their therapeutic potential, particularly for their anti-inflammatory, anticancer, and antimicrobial properties (Win *et al.,* 2015). Recent studies have shown that incubating the natural diterpenoid compound kaempulchraol E with the fungal strain *R. oryzae* KX685359 results in the production of roscorane B (34, Scheme 7) (Elshamy *et al.,* 2020). The biotransformed product 34 was assessed for cytotoxicity against human oral squamous carcinoma cells (HSC-2). Compound 34 demonstrated significant cytotoxic activity, with an IC_{50} value of 54.08 (± 0.05) μM, which was lower than that of the substrate, which had an IC_{50} value of 96.05 (± 0.03) μM.



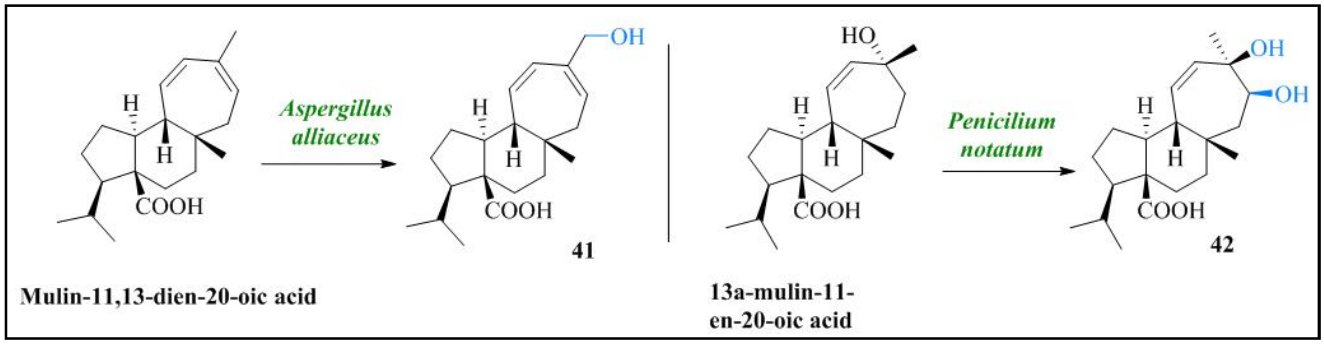
Scheme 7: The structure of the kaempulchraol E 34, biotransformation product produced by the endophytic fungus with *R. oryzae*.

On the other hand, the incubation of 15β-hydroxy-18(4'!3)-abeo-ent-kaur-4(19),16-diene with the fungal strain *Fusarium fujikuroi* resulted in the formation of three biotransformation product: 3α,11β,15β-trihydroxy-18(4 → 3)-abeo-ent-kaur-4(19),16-diene (35), 36 and 37 (Scheme 8) (Fraga, Hernández, and Guillermo 2022). Other researchers also biotransformed diterpenoid compound azorellanol with fungal microorgaisms *A. alliaceus* UI 315 and *M. circinelloides* ATCC 7941 into the three products as 7-deacetyl-azorellanol (38), 4,16-dihydroxy-azorellanol (39) and 2β,16-dihydroxy-14-en-azorellanol (40, Scheme 8) (Herrera-Canché *et al.,* 2023).



Scheme 8: The structure of the 15β-hydroxy-18(4 → 3)-abeo-ent-kaur-4(19),16-diene (35-37) and azorellanol (38-40) biotransformation product produced by the endophytic fungi with *F. fujikuroi* and *A. alliaceus* and *M. circinelloides*.

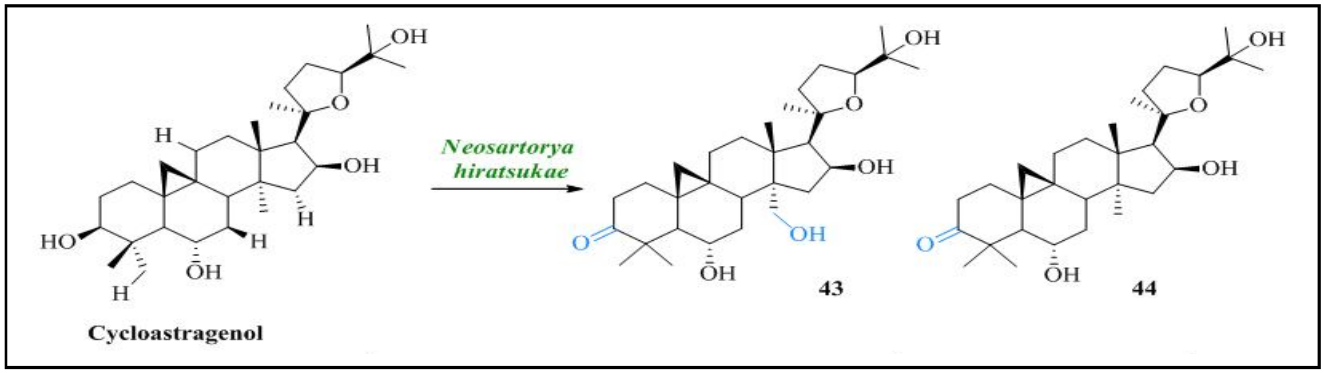
Recently, the microbial biotransformation of mulin-11,13-dien-20-oic acid using *Aspergillus alliaceus* UI 315 afforded a natural products namely 16-hydroxy-mulin-11,13-dien-20-oic acid (41, Scheme 9) (Herrera-Canché *et al.,* 2020). Herrera Canché *et al.* (2023), investigated microbial modification of diterpenoid 13α-mulin-11-en-20-oic acid whith *P. notatum* ATCC 36740 to afford a 13β,14β-dihydroxy-mulin-11-en-20-oic acid (42).

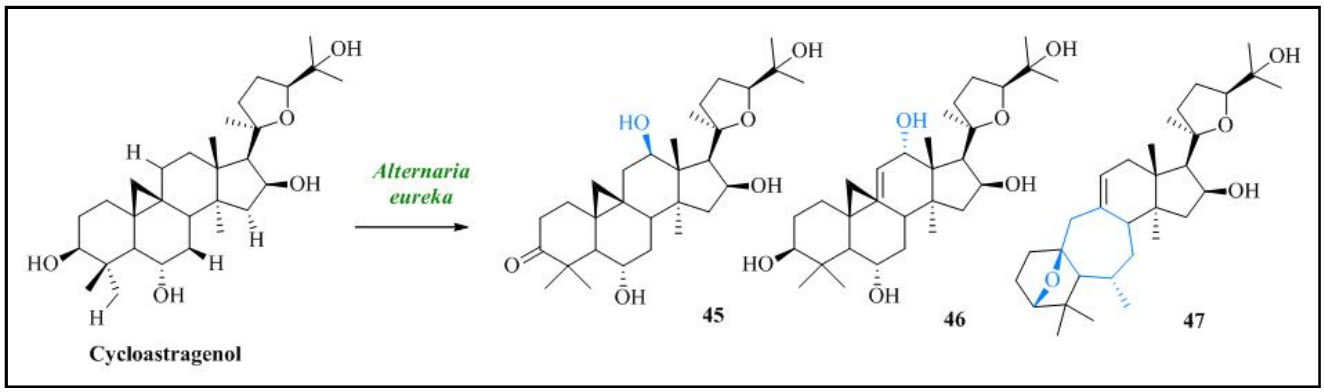


Scheme 9: The structure of the mulin-11,13-dien-20-oic acid (41) and 13α-mulin-11-en-20-oic acid (42) biotransformation product produced by the endophytic fungi with *A.alliaceus* and *P. notatum*.

1.6 Triterpene

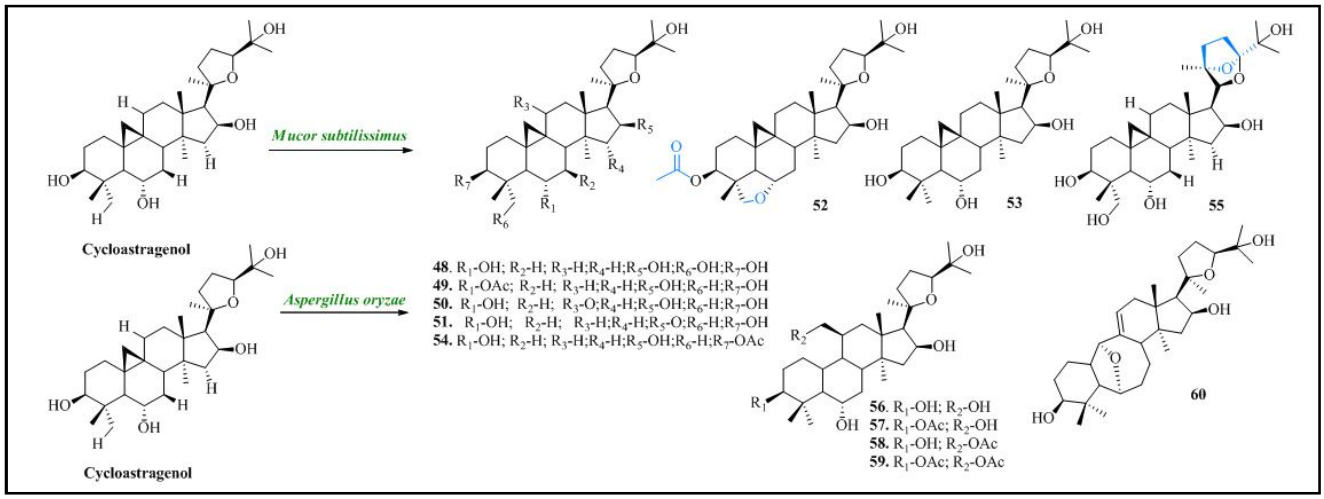
A separate study investigated the microbial biotransformation of cycloastragenol using the endophytic fungi *N. hiratsukae* and *A. eureka*. These fungal strains were isolated from the fresh roots and stems of *A. condensatus* and *A. angustifolius* and were identified through molecular characterization using rDNA ITS sequence analysis. *N. hiratsukae* was found to produce 20(R), 24(S)-epoxy-6α,16β, 25, 30-tetrahydroxycycloartan-3-one (43) and 20(R), 24(S)-epoxy-6α,16β, 25-trihydroxycycloartan-3-one (44) respectively, while *A. eureka* produced three transformation product as 20(R),24(S)-epoxy-3β,6α,12β,16α,25-pentahydroxycycloartane (45), 20(R), 24(S)-epoxy-3β, 6α, 12α, 16β, 25-pentahydroxycy-cloartane (46) and 20(R), 24(S)-6α,16β,25-trihdroxy-3β,10β;20,24-diepoxy-9,10-seco-cycloartan-9(11)-ene (47) (Scheme 10) (Ekiz *et al.,* 2019).





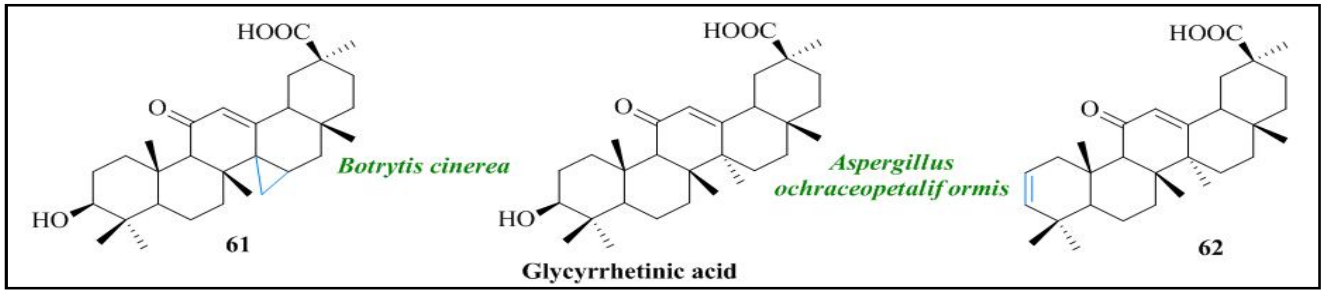
Scheme 10: The structure of the cycloastragenol (43-47) biotransformation product produced by the endophytic fungi *N. hiratsukae* and *A. eureka*.

The microbial biotransformation of cycloastragenol (Scheme 11.) used two fungal species: *M. subtilissimus* AS 3.2456 and *A. oryzae* AS 3.407 produced a total of six new compounds. *M. subtilissimus* could catalyzed hydroxylation and carbonylation reactions meanwhile the fragile 9,19-cyclopropane ring remained intact and formed eight compounds (48-55). Fungal strain *A. oryzae* AS 3.407 preferred to catalyse hydroxylation, acetylation and ring expansion reactions. Five derivation of cycloastragenol were obtained (56-60). These highly specific reactions differ from chemical synthesis, particularly under such mild conditions. The metabolites could significantly extend the lifespan of *C. elegansat* at the concentration of 50 mM. These bio-transformed derivatives of CA could be potential as anti-ageing agents (Chen *et al.,* 2021).



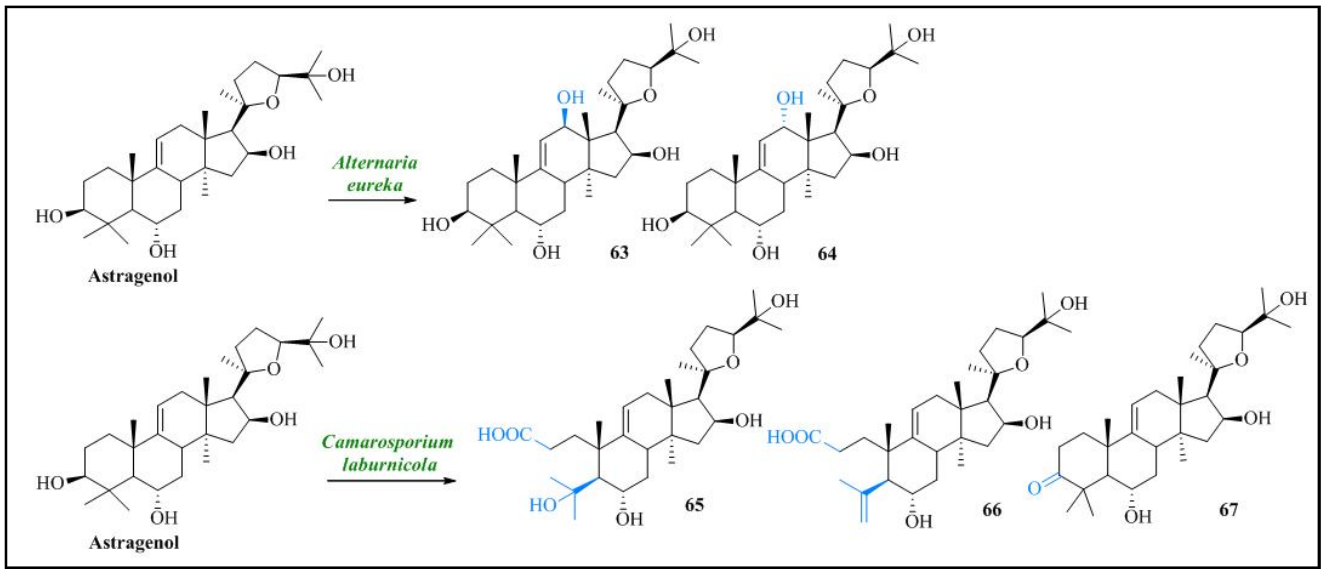
Scheme 11: The structure of the cycloastragenol 48-60 biotransformation product produced by the endophytic fungi with *M. subtilissimus* and *A. oryzae*.

The pentacyclic triterpenoid compound glycyrrhetinic acid was incubated with two fungal strains: *B. cinerea* B05.10 (ATCC 11542) and *A. ochraceopetaliformis* (ATCC 12066). Following the transformation process, two metabolites were obtained: bicyclo [14.15.27] glycyrrhetinic acid (61) and 2-ene-glycyrrhetinic acid (62) (Scheme 12). Additionally, all compounds were screened for anticancer activity against two human cancer cell lines: A549 and HMEC-1. Compound 61 demonstrated a concentration-dependent inhibition of HMEC-1 cell proliferation, with an IC_{50} value of 239.1 μM, while showing negligible cytotoxic effects on A549 cells (Xie *et al.,*).



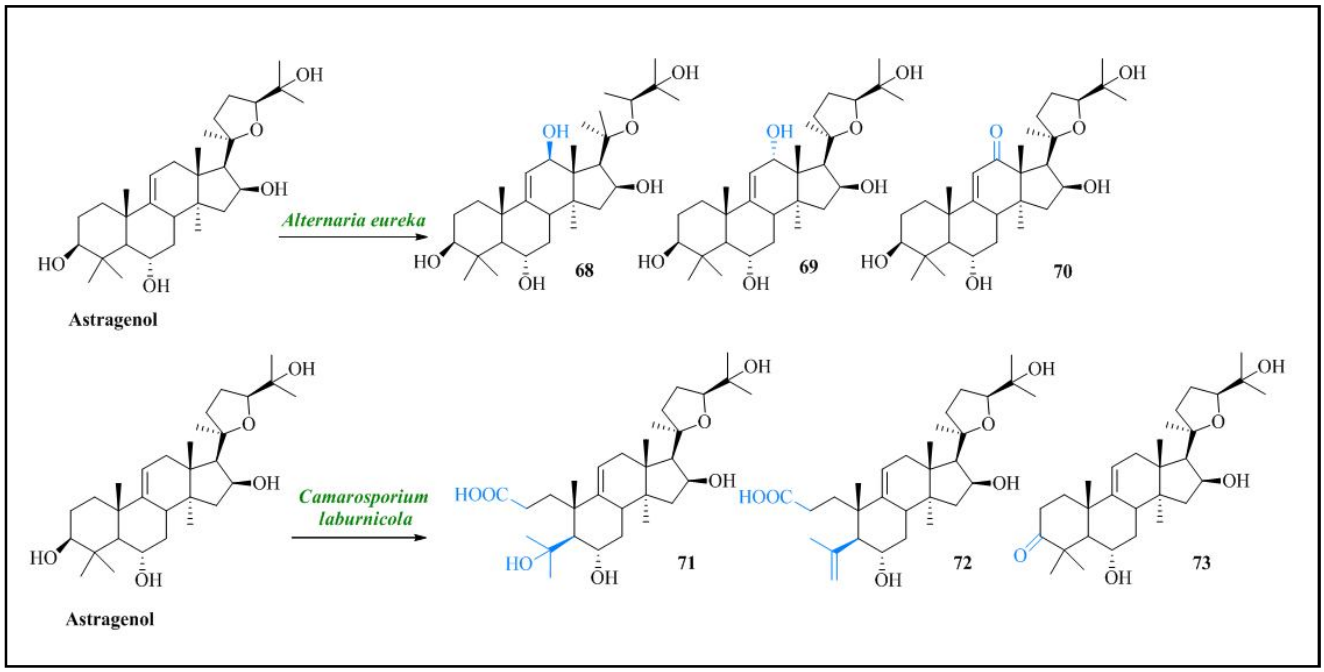
Scheme 12: The structure of the glycyrrhetinic acid (61-62) biotransformation product produced by the endophytic fungi *B. cinerea* and *A. ochraceopetaliformis*.

The microbial biotransformation of astragenol was conducted using the endophytic fungi *A. eureka* and *C. laburnicola*. Fungal strains were isolated from the fresh roots of *A. angustifolius* and identified through molecular analysis using rDNA ITS sequence analysis. *A. eureka* produced four new transformation products as 20(R), 24(S)-epoxy-3β, 6α,12β,16β,25-pentahydroxylanost 9(11)-ene33 (63) and 20(R), 24(S)-epoxy-3β, 6α,12α,16β,25-pentahydroxylanost-9(11)-ene (64). Compounds, including the 3,4-seco derivatives of astragenol (65 and 66) and 20(R), 24(S)-epoxy-6α,16β,25-trihydroxylanost-9(11)-en-3-one (67), were isolated from the biotransformation of astragenol using *C. laburnicola* (Scheme 13) (Ekiz *et al.,* 2019).



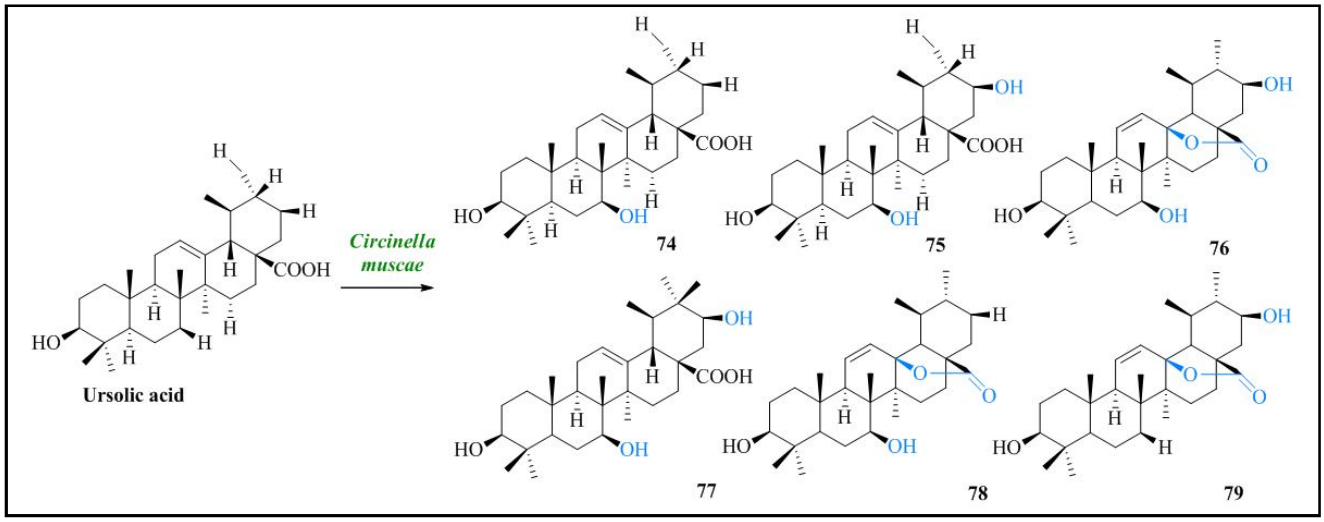
Scheme 13: The structure of the astragenol (63-67) biotransformation product produced by the endophytic fungi *A. eureka* and *C. laburnicola*.

Astragenol, a natural compound widely used in herbal medicine, particularly in Asia, is extracted from the roots of the plant *A. membranaceus*. Ekiz *et al.* (2019) reported the biotrans-formation of astragenol by the fungal strains *A. eureka* and *C. laburnicola*. The biotransformation resulted in the formation of six distinct products namely, 20(R),24(S)-epoxy-3β, 6α,12β,16β,25-pentahydroxylanost-9(11)-ene (68), 20(R),24(S)-epoxy-3β,6α,12α, 16β,25-pentahydroxylanost-9(11)-ene (69), 20(R),24-(S)-epoxy-3β, 6α,16β,25-tetrahydroxylanost-9(11)-en-12-one (70), (71), (72), and 20(R),24(S)-epoxy-6α,16β,25-trihydroxylanost-9(11)-en-3-one (73) (Scheme 14).



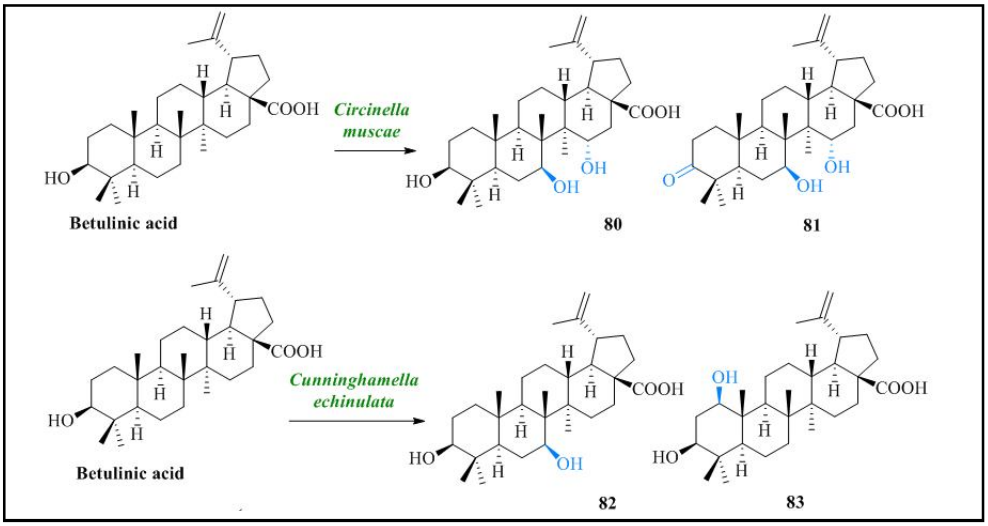
Scheme 14: The structure of the astragenol (68-73), biotransformation product produced by the endophytic fungi with *A. eureka* and *C. laburnicola*.

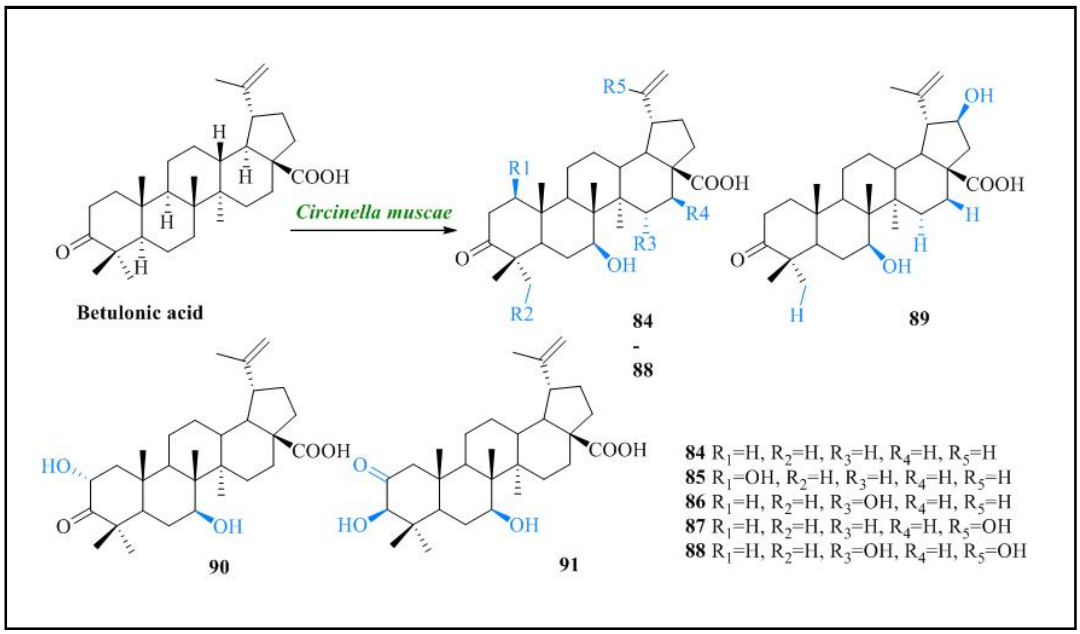
The selective carbonylation, lactonisation, carboxyl reduction and hydroxylation bioconversion of ursolic acid with fungal strain *Circinella muscae* CGMCC 3.2695 yielded six transformation products (79-84, Scheme 15) namely 3β,7β,21β-trihydroxy-ursolic acid (74), 21β-hydroxyl-A-homo-3*a*-oxa-urs-12-en-3-one-28-oic acid (75), 1β, 3β, 21bβ-trihydroxyurs-12-en-28-oic acid (76), 3β,7β, 21β-trihydroxy-urs-11-en-28-oic acid-13-lactone (77), 3β,21β-dihydroxy-urs-11-en-28-oic acid-13-lactone (78), 7β,21b-trihydroxy-urs-11-en-28-oic acid-13-lactone (79). Moreover, anti-neuroinflammatory activity of all metabolites were investigated, compounds 79 and 82 showed potential inhibitory activity (Chu *et al.,* 2022).



Scheme 15: The structure of the ursolic acid 74-79 biotransformation product produced by the endophytic fungus with *C. muscae*.

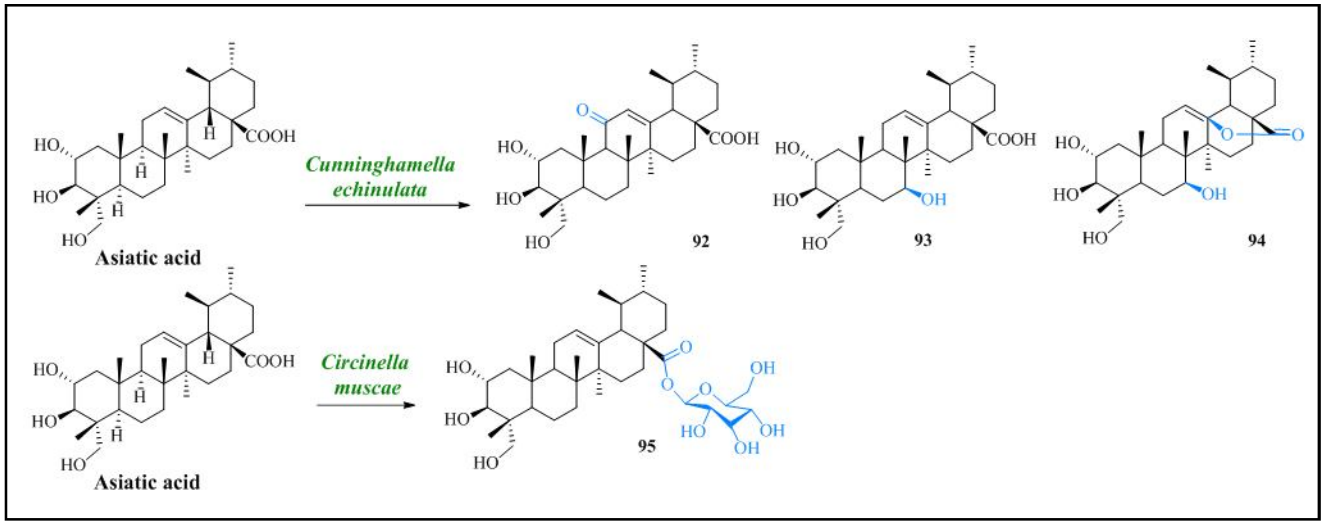
Pentacyclic triterpene betulinic acid transformed by two most active fungal strains *Circinella muscae* CGMCC 3.2695 and *Cunninghamella echinulata* CGMCC 3.970 to give four biotransformation products namely 3β,7β,15α-trihydroxy-lup-20 (29)-en-28-oic acid (80), 7β,15α-dihydroxy-3-oxo-lup-20 (29)-en-28-oic acid (81), 3β,7β-dihydroxy-lup-20 (29)- en-28-oic acid (82), and 1β,3β-dihydroxy-lup-20 (29)-en-28-oic acid (83) (Scheme 16) (Chen, Song, *et al.,* 2021). Compounds 80 and 82 inhibited satisfactory against NO with IC_{50} values of 26.62 and 23.62 μM respectively. Betulonic acid is a naturally occurring pentacyclic triterpenoid derived from betulin, a compound abundantly found in the bark of birch trees (*Betula* genus). As a lupane-type triterpenoid and a direct derivative of betulinic acid, betulonic acid has garnered significant attention due to its diverse pharmacological potential. Research highlights its broad spectrum of biological activities, including anticancer, antimicrobial, antiviral, and anti-inflammatory effects. Notably, microbial transformation of betulonic acid by the cell culture of *C. muscae* CGMCC 3.2695 resulted in the production of eight distinct biotransformation metabolites (84-91, Scheme 16), namely: 3-oxo- 7β-hydroxy-lup-20 (29)-en-28-oic acid (84), 3-oxo-7β,23-dihydroxy-lup- 20 (29)-en-28-oic acid (85), 3-oxo-7β,15α-dihydroxy-lup-20 (29)-en-28- oic acid (86), 3-oxo- 7β,30-dihydroxy-lup-20 (29)-en-28-oic acid (87), 3- oxo-7β,15α,30-trihydroxy-lup- 20 (29)-en-28-oic acid (88), 3-oxo-7β,21β- dihydroxy-lup-20 (29)- en-28-oic acid (89), 3-oxo-2α,7β-dihydroxy-lup- 20 (29)-en-28-oic acid (90), and 2-oxo-3β,7β-dihydroxy- lup-20 (29)-en- 28-oic acid (91). Additionally, compounds 84, 85, 82, 88, 89 and 90 demonstrated promising anti-neuroinflammatory activities against LPS-induced BV-2 cells, with IC_{50} values of 35.17 ± 3.87, 14.85 ± 1.94, 13.14 ± 2.15, 30.71 ± 1.21, 9.56 ± 3.59 and 66.28 ± 5.36 μM respectively (Lu *et al.,* 2022).





Scheme 16: The structure of the betulinic acid 80-91 biotransformation product produced by the endophytic fungi with *C.muscae* and *C. echinulata*.

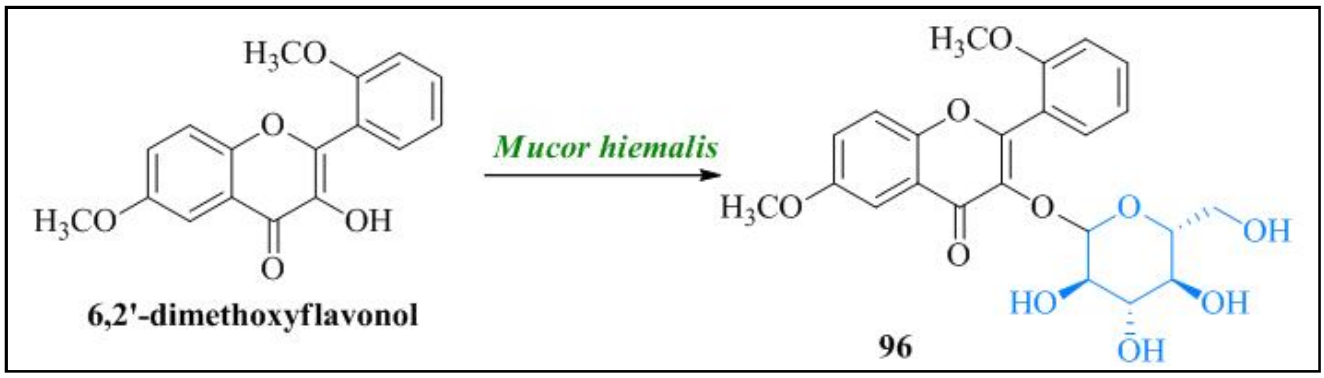
The biocatalysis of asiatic acid with two fungal strains, *C. echinulata* CGMCC 3.970 and *C. muscae* CGMCC 3.2695, was investigated by Wu *et al.* (2023). The strain *C. echinulata* CGMCC 3.970 efficiently transformed asiatic acid through regioselective hydroxylation, carbonylation, and lactonization to yield three metabolites: 11-oxo-2α,3β,23-trihydroxyurs-12(13)-en-28-oic acid (92), 2α,3β,7β,23-tetrahydroxyurs-12(13)-en-28-oic acid (93), and 2α,3β,23-trihydroxyurs-11(12)-en-13β,28-lactone (94) (Scheme 17). *C. muscae* efficiently transformed asiatic acid by selectively catalyzing hydroxylation, acetylation, and glycosylation into asiatic acid 28-O-β-D-glucopyranoside (95). All transformation products were measured for their anti-neuroinflammatory activities on LPS-induced NO production in BV-2 cells. Metabolites 92, 93, and 95 displayed moderate effects with IC_{50} values of 38.56, 26.33, and 49.86 mM, respectively.



Scheme 17: The structure of the asiatic acid 92-95 biotransformation product produced by the endophytic fungu with *C. echinulata* and *C. muscae*.

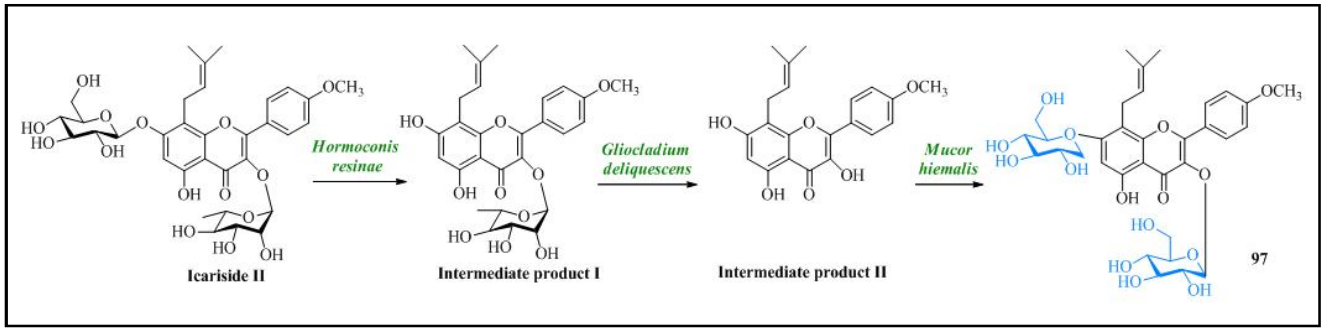
1.7 Flavonoids

Flavonoids are polyphenolic compounds present in various plant species. Numerous bioactive natural compounds derived from flavonoids exhibit potent antimicrobial, antioxidant, antidiabetic, and anticancer properties. Biotransformation, a process involving microbial or enzymatic modification of flavonoids, enhances their pharmacological potential by improving bioactivity, solubility, and absorption (Wu, Lv, *et al.,* 2023). The microbial transformation of the compound 6,22 -dimethoxy-flavonol using *Mucor hiemalis* resulted in the production of a novel metabolite, 6,22 -dimethoxyflavonol-3-O-β-D-glucopyranoside (96) (Scheme 18) (Kim *et al*., 2020).



Scheme 18: The structure of the 6,22 -dimethoxyflavonol 96 biotransformation product produced by the endophytic fungu with M. hiemalis.

Incubation of icariin II with three species of fungal strains including *H. resinae*, *M. ramanniana* var. *angulispora* and *G. deliquescens* afforded a biotransformaton product icaritin-3,7-d-β-d-diglucopyranoside (97). Three metabolic pathways were proposed for this bioconversion. The first pathway was using *H. resinae* and *M. ramanniana* var. *angulispora* produced compound intermediate I, after that intermediate I transformed by *G. deliquescens* to afford compound intermediate II. The final metabolic pathway used *M. hiemalis* involved glycosylated product as described in the (Scheme 19) (97) (Han et al., 2022). Evaluation of anticancer activity of icariin II and biotransformation compounds using the MTT assay. Compound exhibited potent cytotoxic activity against human cancer cell lines A549, A375P, and MCF-7, with IC_{50} values of 41.64 ± 5.09, 39.78 ± 1.60, and 39.83 ± 1.89 μM, respectively.

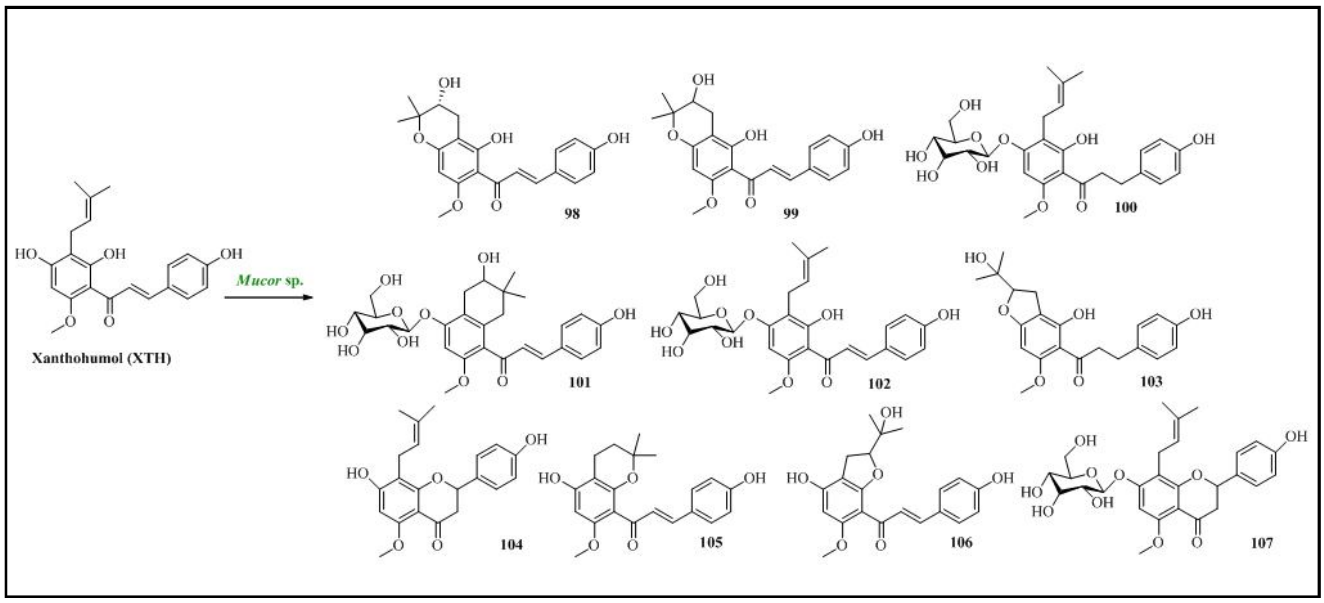


Scheme 19: The structure of the icariin II (97) biotransformation product produced by the endophytic fungi with *H. resinae*, *M. ramanniana* var. *Angulispora* and *M. hiemalis*.

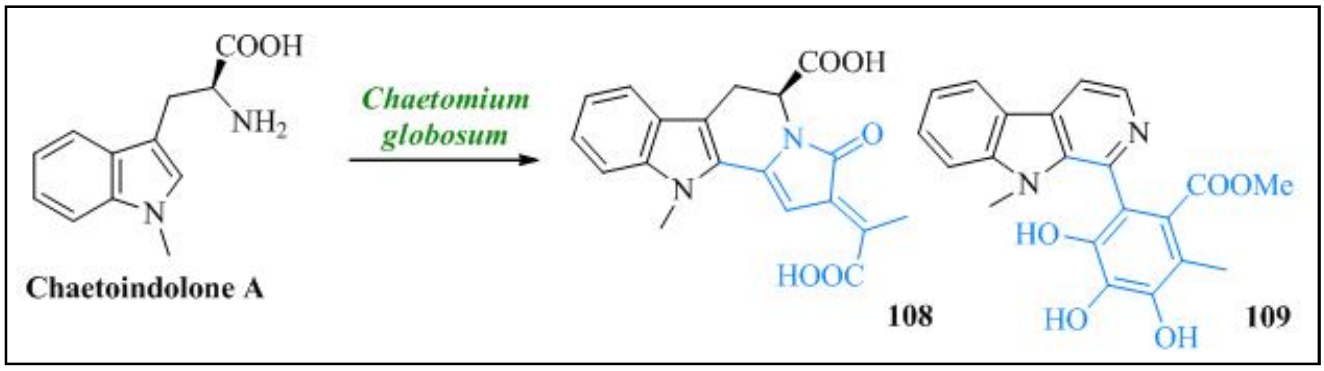
Xanthohumol, a prenylated flavonoid primarily found in hops (*H. lupulus*), has attracted considerable attention due to its diverse biological and pharmacological properties. This compound exhibits a broad spectrum of bioactive effects, including antimicrobial, antioxidant, antiviral, anti-inflammatory, anticancer, and antidiabetic activities. Ongoing research explores its therapeutic potential, particularly in drug development within the fields of pharmacology and medicinal chemistry. A recent study by Xiao *et al.,,* 2024, reported the biotransformation of xanthohumol using the fungal microorganism *Mucor* sp., resulting in the production of two novel (98 and 100) metabolites namely (23 R)-dihydroxanthohumol B (98) and xanthohumol L 42 -O-β-Dglucopyranoside (100) along with eight previously identified metabolites (99-107): xanthohumol B (99), α, β-dihydroxanthohumol 42 -O-β-D-glucopyranoside (101), xanthohumol 42 -O-β-D-glucopyranoside (102), 23 -(23 -hydroxyisopropyl)-dihydrofurano[43 ,53 :32 ,42]22 ,4-dihydroxy-62 -methoxy α, β-dihydrochalcone (103), (Scheme 20) isoxanthohumol (104), 23 ,23 -dimethyl-33 ,43 -dihydro-(2H)-pyrano[53 ,63 :22 ,32]4,42 -dihydroxy-62 -methoxychalcone (105), 23 -(23 -hydroxyisopropyl)-23 ,33 -dihyrofurano[43 ,53 :22 ,32]4,42 -dihydroxyl-62 -methoxychalcone (106), 5-methoxy-8-prenylnaringenin 7-O-β-D-glucopyranoside (107) (Xiao *et al.,*). All metabolites were evaluated for their anticancer activity against three human cancer cell lines: A375P, MCF-7, and A549. Among them, compounds 100, 103, and 105 exhibited significant anticancer activity against all tested cell lines.

1.8 Alkaloid and nitrogen compound

Alkaloids are nitrogen-containing secondary metabolites found in plants, microorganisms, and animals, known for their diverse biological activities, including antimicrobial, anticancer, antidiabetic, and neuroactive effects. Biotransformation using fungal microorganisms can enhance their pharmacological potential by modifying functional groups, increasing solubility, and improving bioavailability (Huang *et al.,* 2022). Indole alkaloid chaetoindolone A, microbial modified tby the marine fish-derived fungus *Chaetomium globosum* $1C_{51}$, produced two biotransformation products as chaetogline A (108) and Chaetogline B (109) (Scheme 21). Furthermore, the biotransformation products were evaluated for their *in vitro* and *in vivo* plant-pathogenic activity against the rice-pathogenic bacteria *Xanthomonas oryzae* pv. *oryzae* (Xoo). Compounds exhibited significant activity against *X. oryzae* pv. *Oryzae* (Yan *et al.,* 2019).

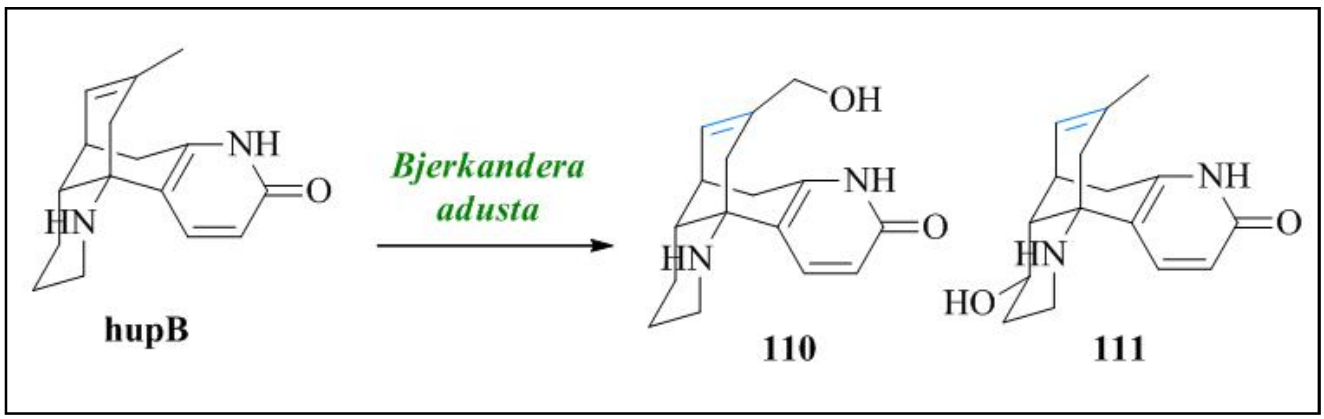


Scheme 20: The structure of the xanthohumol (98-107) biotransformation product produced by the endophytic fungus with *Mucor* sp.



Scheme 21: The structure of the chaetoindolone A (108-109) biotransformation product produced by the endophytic fungus *C. globosum*.

Huperzine B (HupB) is a natural compound belonging to the alkaloid class, derived from the medicinal plant *H. serrata*. It has been investigated for its potential effects on the nervous system, particularly as an acetylcholinesterase (ACHE) inhibitor. Recently, Zhang *et al.* (2019), incubated huperzine B (HupB) with the fungus *B. adusta* CCTCC M 2017159, resulting in the production of two metabolites: 16-hydroxyhuperzine B (110) and carinatumin B (111) (Scheme 22).

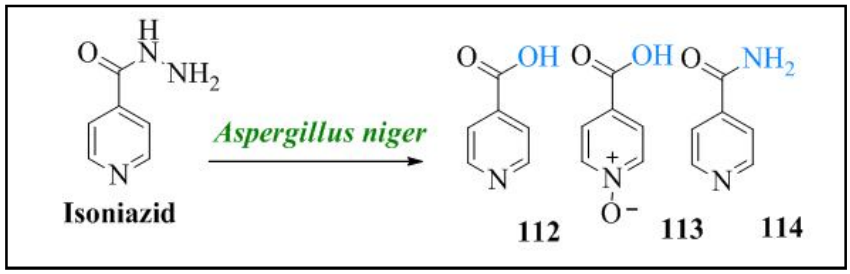


Scheme 22: The structure of the HupB (115-116), biotransformation product produced by the endophytic fungus with *B. adusta.*

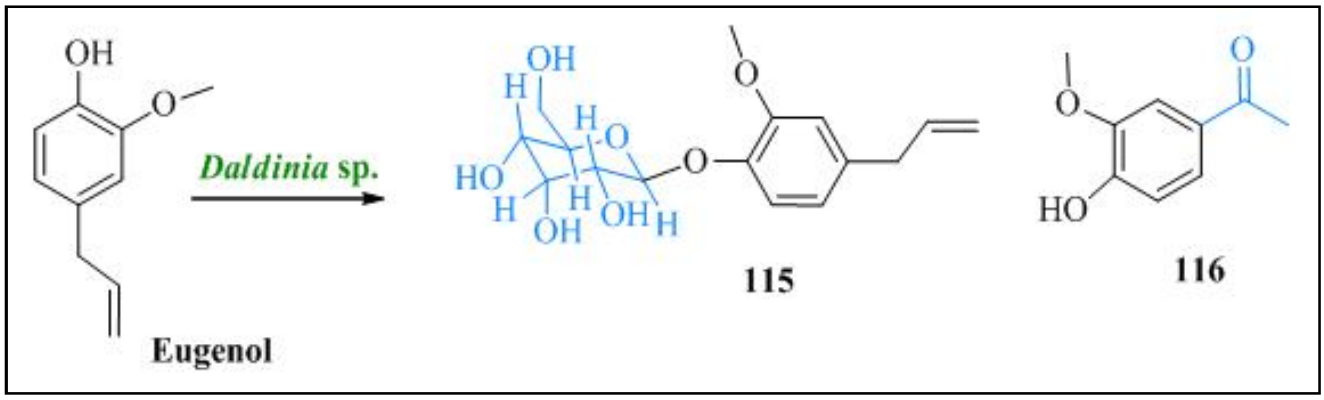
Isoniazid transformation by *A. niger* NRRL 328 produced three compounds including isonicotinic acid (112), isonicotinic acid N-oxide (113), and isonicotinamide (114) (Scheme 23). The antituberculosis activity of the starting compound isoniazid and all its biotransformation products was evaluated. The results showed that isoniazid and all its metabolites inhibited antituberculosis activity against the DS strain of *M. tuberculosis* ATCC 25177/H37Ra, with MICs of 0.88, 63.49, 0.22, and 15.98 µM, respectively (Ragab *et al.,* 2023). Furthermore, all modified compounds were screened for their antituberculosis activity against *Mycobacterium tuberculosis* strains. The metabolites exhibited moderate activity, with minimum inhibitory concentrations (MICs) of 63.49, 0.22, 15.98, and 0.88 mM, respectively.

1.9 Others

In a previous study, the microbial transformation of the natural compound eugenol was conducted using the endophytic fungus *Daldinia* sp. III MF4010, which was isolated from the fresh leaves of *R. officinalis*. After biotransformation processes yielded two modified metabolites as eugenol-β-D-glucopyranoside (115) and vanillin (116) (Scheme 24) (Lone *et al.,* 2023).



Scheme 23: The structure of the isoniazid 112-114 biotransformation product produced by the endophytic fungu with A. niger.



Scheme 24: The structure of the eugenol 115-116 biotransformation product produced by the endophytic fungu with Daldinia sp.

2. Conclusion

Biotransformation is an effective strategy for modifying flavonoids, alkaloids, terpenoids, steroids, and polyphenols, enhancing their solubility, bioavailability, and pharmacological efficacy. Microbial and enzymatic processes, including hydroxylation, methylation, glycosylation, and oxidation, are essential for generating bioactive metabolites with enhanced antimicrobial, anticancer, antidiabetic, and antioxidant properties. This review highlights the bioconversion of 27 substrates by 23 fungal genera, leading to the identification of 116 biotransformation products. Among these, the most active endophytic fungi were from the genera *Aspergillus*, *Mucor*, *Circinella*, *Fusarium*, and *Penicillium*. Biotransformation enhances the pharmacological potential of natural compounds, increasing their effectiveness in medicine, pharmaceuticals, and agriculture. Its key applications include the development of novel drugs with improved bioactivity, bioavailability, and therapeutic efficacy.

Conflict of interest

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

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