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Biotransformation: A Novel Approach of Modulating and Synthesizing Compounds

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ABSTRACT

Transformation of potential compounds into utilizable and beneficial forms is often cost involving and time consuming. Chemical transformation though was an existing opportunity catering our needs but due to environmental impacts and cost-benefit ratio analysis it proved futile and a new branch of transformation came into existence termed as biotransformation. Biotransformation is an excellent opportunity of tailoring compounds to cater our needs in a simple and is an eco-friendly approach. Biotransformation allows conversion of one component to another compound by application of biological systems. Fermentation based biotransformation of plant extract is a well-established world-wide standard technique used to maximize shelf-life, nutritional and organoleptic properties and to eliminate harmful substances from primary food substrates. Biotransformation by microbes has grown greatly from a small involvement in highly active fields of green chemistry, including the preparation of pharmaceutical drugs, in recent years. In addition fermentation processes have been targeted and optimized to enhance the production of active microbial metabolites using sufficient or suitable nutrients and with the correct microbial target for functional benefits. At present, significant attention has been given to biotransformation technology worldwide to develop medicines through the processing and enrichment of additional medicinally essential bioactive metabolites including terpenes, alkaloids, phenols, flavonoids and saponins. Biotransformation utilizing various biological systems can be used to modulate and in the enhancement of bioactive compounds in an environment promising way. Biotransformation is assumed to play a key role in green chemistry in future because of its sustainable approach. This review represents an overview of biotransformation techniques and its applications in a nutshell.

Keywords- Biotransformation, Bioconversion, Microbial transformation, Solid State Fermentation.

I. INTRODUCTION

Biotransformation processes are interesting biological tools for development of various potent drugs and for the structural modification of natural products with complex chemical structure (De Sousa *et al.,* 2018). Biotransformation allows conversion of one component to another compound by application of biological system (Smitha *et al.,* 2017). Biotransformation is a field of biotechnology that has attracted significant interest in recent years owing to the negative influences of chemical transformation on the environment. It is the ability of plant cell to convert inexpensive precursors into more desirable and valuable tailored final products. . It can also be characterized as the chemical transformation that is catalyzed by the micro-organism or its enzymes (Khirwadkar*et al.,* 2014). Fermentation based biotransformation of plant extract is a well-established world-wide standard technique used to maximize shelf-life, nutritional and organoleptic properties and to eliminate harmful substances from primary food substrates. In addition fermentation processes have been targeted and optimized to enhance the production of active microbial metabolites using

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sufficient or suitable nutrients along with using the correct microbial target for functional benefits (Kaprasob et *al.,* 2017). Biotransformation by microbes has grown greatly from small involvements in highly active fields of green chemistry, including the preparation of pharmaceutical drugs, in recent years. Isolated compounds are commonly available in limited quantities. Microbial biotransformation thus is an effective way of addressing supply issues in clinical trials and of selling the drug in bulk quantities from the natural products procurement point of view.. Biotransformation involves structural modification of chemicals such as primary metabolites and secondary metabolites. The conversion of molecules from one type to another is often correlated with a transition (increase, decrease or minor change) in pharmacological behavior ((Khirwadkar*et al.,* 2014). Processes of biotransformation often play a key role in the production or enhancement of drugs (Sousa *et al.,* 2018). Biotransformation also plays vital role in development of novel anti-cancer drugs (Gao *et al.,* 2013).

New compounds may be formed or the content of active components may be altered through microbial fermentation of traditional Chinese medicine substances (Li *et al.,* 2006). Biotransformation is an important chemical approach in green chemistry which aims at the maximum possible productivity with minimum waste generation and lowest detrimental environmental effects (Bainchini *et al.,* 2015).

Biotransformation using Solid-state fermentation (SSF) has been successfully used to convert agro-industrial residues and plant materials into valuable compounds, including bioactive phenolic compounds (Liu *et al.,* 2017). Biotransformed plant extracts, not only provide nutrition but also provide health benefits in food due to the presence of various antioxidants (Zafar*et al.,* 2016). At present, significant attention has been given to biotransformation technology worldwide to develop medicines through the processing and enrichment of additional medicinally essential bioactive metabolites including terpenes, alkaloids, phenols, flavonoids and saponins (Mutafova *et al.,* 2016).

II. TYPES OF BIOTRANSFORMATION

Biotransformation can be categorized into two type's namely enzymatic transformation and non enzymatic transformation as shown in fig.1. Enzymatic transformation is further classified into Microsomal and Non-microsomal transformation.

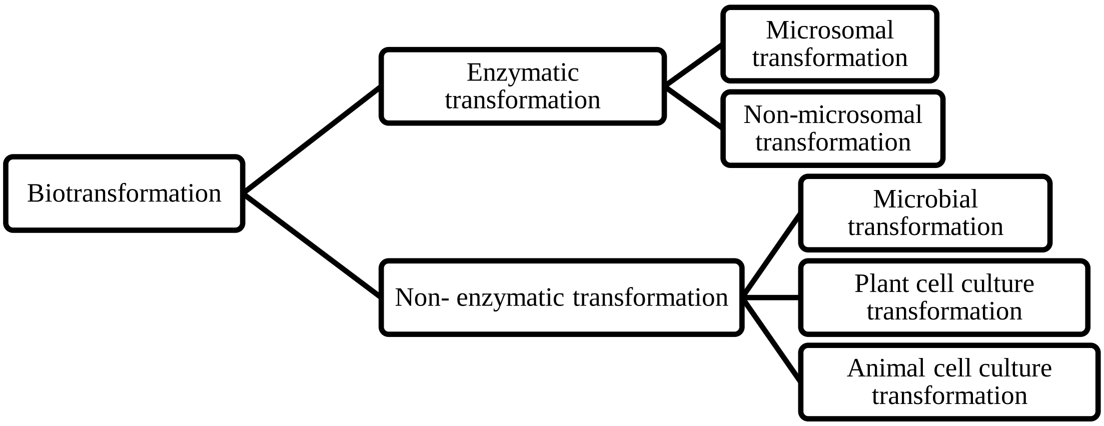

Figure 1: Types of Biotransformation

Enzymatic transformation is a biotransformation process that occurs due to different enzymes found in the body of organisms. Microsomal biotransformation is caused by enzymes present in smooth endoplasmic reticulum lipophilic membranes. The enzymes that are found within the mitochondria provide non-microsomal biotransformation (Smitha *et al.,* 2017). Non-enzymatic transformation is categorized into three type's namely microbial transformation, plant cell culture transformation and animal cell culture transformation. Microbial biotransformation involves utilization of living microbes for the purpose of biotransformation whereas in plant cell culture transformation, plant parts and in animal cell culture transformation animal organs mostly liver cells are used as biotransformation machineries (Yousuf *et al.,* 2019).

III. APPLICATIONS OF BIOTRANSFORMATION

Biotransformation is an important chemical approach in green chemistry which aims at the maximum productivity with minimum waste generation and lowest environmental effects. It has got various potent applications in diverse field'snaming a few fields like pharmaceuticals, waste management, veterinary uses etc. The diverse applications of biotransformation have been elucidated in figure 2.

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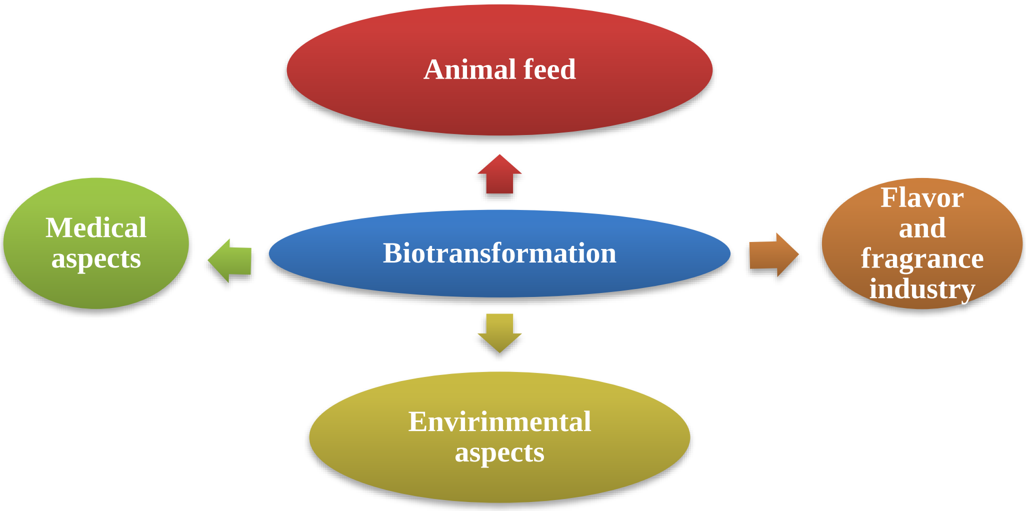

Figure 2: Applications of Biotransformation

Animal feed preparation:

Lignocellulose is a major component of agricultural waste which contains hemicellulose, cellulose and lignin in variable amount depending upon crop type (Nurika *et al.*, 2019). Lignocelluloses can act as important substrates for obtaining value added compounds by using fungal intracellular enzyme (Asgher *et al.*2016). For example, Nurika *et al.*, 2019 demonstrated biotransformation of five tropical waste materials (rice straw, cacao pod, corn cob, corn leaves and sugarcane baggasse) by using brown rot fungus *Serpula lacrymnus.* Biotransformed products formed were found to have high amount of total soluble sugars and total soluble phenols.

Zepf and Jin, 2013 studied solid state fermentation (SSF) by using fungal strains *Aspergillus oryzae* DAR 3699, *Aspergillus oryzae* RIB 40 and *Trichoderma reesei* RUT C30 for bioconversion of red grape marc (RGM) into protein enriched animal feedstock. The protein content increased from 7% to 27% in 5 days of fermentation. Biotransformation technique can be utilized to reduce anti-nutritional factors in plant materials to convert food material suitable for animal consumption (Torres-León *et al.*, 2018). Pinela *et al.*, 2020 employed dikaryotic strain DK3174 and the monokaryotic strain P6 (Mk) of *Pleurotus sadipus* for biotransformation of rice and sunflower side -streams as substrates for conversion of lignocellulosic materials into animal feed with reduced polyphenol content.

Plantain plant residues are made up of lignocellulosic materials which are composed of hemicellulose, cellulose, lignin and other compounds (Cadena Ch *et al.*, 2017). Biotransformation using yeast slurry and digestive juices obtained from African snail (*Archachatina marginata*) has been successfully used to convert plantain (*Musa paradisiaca*) pseudostem fibres (PPS) into valuable poultry feed containing improved carbohydrate, protein quality, mycotoxins, and antioxidant properties (Amadi *et al.*,2018). Moreover, Özyurt et al., 2017 employed Lactic acid bacteria (LAB) fermentation to convert fish waste into easily digestible animal feed enriched in amino acids composition and antioxidant activity.

Biotransformation for obtaining flavor and fragrance compounds:

White biotechnology has been used for production of aroma compounds in bulk amounts from simple molecules by using biotransformation and de novo synthesis (Bicas *et al.*, 2016, Bution, *et al.*, 2015). α- pinene and β-pinene are found abundantly in essential oils of many plants (Salehi *et al*., 2019). They have wide application in chilled dairy products, candy preparation, bakery industry, cosmetic sector etc. (kashi *et al.*, 2007, Salehi *et al.*, 2019). Kashi *et al.*, 2007 reported the biotransformation of β-pinene into α- pinene by bacterial strain isolated from *Ferula* galbanum soil. Molina *et al.*, 2019 optimized biotransformation process to obtain high amount of R-(+)-α-terpineol from R-(+)-limonene by using *Sphingobium sp*. Hong and his coworkers, 2015, studied bioconversion of (-)-α-pinene and geraniol to oxygenated productsviz. α-terpineol and (-)-*trans*-p-menthane-3,8-diol using *Polyporus brumalis.*

Vanillin is an important phenolic aldehyde obtained naturally from pods of vanilla orchids and widely used in food, beverage, and cosmetics as a flavoring agent (Chen *et al.*, 2016). Singh *et al.*, 2019 utilized *Bacillus safenis SMS1003*strainfor bioconversion of eugenol into vanillin. Similarly, Chen *et al.*, 2016 reported microbial bioconversion of ferulic acid into vanillin by *Bacillus subtilis* BS-7. Jun *et al.*, 2015 described a new metabolic route for de novo synthesis of vanillin by *Escherichia coli* and using L-tyrosine, glucose, xylose and glycerol as carbon sources. In another study conducted by Ma and his coworkers, 2014 employed solid-liquid two phase partioning

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bioreactor system to increase the bioconversion of ferulic acid to vanillin using *Amycolatopsis spp.* Several other studies reported utilization of genetically engineered strains for enhanced production of vanillin (Fleige and Steinbüchel , 2014).

For example, furuya *et al.,* 2015 employed engineered *E.coli* using two stage bioprocess for bioconversion of ferulic into vanillin. In first stage, E. coli expressing a gene coding for *Fdc* from *Bacillus pumilus*,converted ferulic acid to 4-vinylguaiacol which was then converted into vanillin in second stage by using E. coli expressing gene encoding for *Cso2* from *Caulobacter segnis*. Chakraborty *et al.,* 2016, investigated production of vanillin from ferulic acid as sole substrate by engineered *E.coli* top 10. Furthermore, Chakraborty *et al.,* 2017 utilized genetically engineered *Pediococcus acidilactici* BD16 (fcs +/ech +) for biotransformation of ferulic acid into vanillin using rice bran as substrate.Moreover , it has been reported in study that limonene-1-diol, α-terpineol, α-tocopherol, dihydrocarveol, carvone and valencene in biotransformed orange extracts using diaporthe sp. showed significant increase in antioxidant activity(Bier *et al.*,2019).

2-Phenylethanol is an aromatic compound which has wide applications in perfume industries, cosmetics and food industries due to its rose like aroma (Hua *et al.,* 2011). Many studies reported utilization of genetically modified microorganisms for production of 2-phenylethanol by biotransformation of phenylalanine. For example, kim *et al.,* 2014 employed genetically engineered *Saccharomyces cerevisiae* for bioconversion of L-Phenylalanine into 2-Phenylethanol. Similarly, Guo and his coworkers, 2017 reported production of 2-phenylethanol from L- phenylalanine by engineered *Escherichia coli.* Moreover, it was found that *Yarrowia lipolytica*was capable of biotransforming L-phenylalanine into 2-phenylethanol (Celińska *et al*., 2013).

Soares *et al.,* 2017 recently reported production of cyclic ester lactone, γ-decalactone by *Lindnera saturnus* asnd crude glycerol as substrate. Similarly, many studies reported higher production of γ-decalactone by *Yarrowia lipolytica* and *Lindnera saturnus* using crude castor oil as substrate (Gomes *et al.*2013, De Andrade et al., 2017). An *et al.,* 2013 reported biotransformation of 10-hydroxystearic acid into γ-decalactone by permeabilized cells of *Waltomyces lipofer.* Furthermore, Jo and his coworkers, 2014 reported biotransformation of 10-hydroxy-12(Z)-octadecenoic into γ-decalactone by *Candida boidinii.* A phenylpropanoidRasberry ketone [4-(4-hydroxyphenyl) butan-2-one], is a most important and expensive flavoring compound obtained from many fruits like raspberries, grapes, blackberries and vegetables. Lee *et al.,* 2016 studied biotransformation and de novo synthesis of raspberry ketone from p-coumaric acid by using an industrial strain of Saccharomyces *cerevisiae.*

A sesquiterpene Nerolidol, has wide biological and technical applications in development of drugs, flavors and it also acts as precursor in synthesis of E/K1 (Peng *et al.,* 2017). Sonntag *et al.,* 2015 reported production of α-humulene using a metabolically engineered *Methylobacterium extorquens* AM1 expressing gene from *Zingiber zerumbet* encoded *for* α-humulene synthase, in amalgamation with FPP synthase from *Sacharromyces cerevisiae* and methanol as a sole carbon source.furthermore , Ibrahimi *et al*.,2020 reported synthesis of 13 new volatile compounds by biotransformation of genetically modified hairy roots of *Hypericum perforatum* (L.) grown with 14 basidiomycetes as source of carbon and nitrogen.

Nunes *et al.,* 2013 investigated production of p-menthane-2, 8, 9-triol by *Lasiodiplodia theobromae* and *Mucor Circinelloides using* R-(-)-carvone as substrate . Later, Goretti *et al.,* 2013 reported bioconversion of flavoring compounds(4R)-(-)-carvone and (1R)-(-)-myrtenal into myrtenol,dihydromyrtenals and dihydro-myrtenols by *Candida freyschussii* and *Kazachstania spencerorum.* Omarini *et al.*, 2016 reported biotransformation of 1,8-cineole into two novel compounds namely 1,3,3-trimethyl-2-oxabiciclo[2.2.2]octan-6-ol and 1,3,3-trimethyl-2-oxabiciclo[2.2.2]octan-6-one by solid state fermentation of edible mushrooms *Pleurotus ostreatus* and *Favolus tenuiculus* using *Eucalyptus cinerea* waste as substrate.

Medeiros *et al.*, 2021 studied fungal biotransformation of R-(+)-limoneneinto limonene-1, 2-diol which has potential application in chemotherapy, treatment of bronchitis and as flavoring agent in food and beverage industry using fungal strain *Colletotrichum nymphaea* CBMAI 0864 and ethyl acetate as solvent with sequential extraction method for maximum recovery of Product.

Biotransformation of antibiotics:

In a research by Qiao *et al.,* 2007, theyreportedthat Cinobufagin was biotransformed into 5 metabolites namely 12a -hydroxybufagin, 11a -hydroxybufagin, 12b -hydroxy-desacetylcinobufagin, 3-oxo-12a -hydroxybufagin and 12b –hydroxybufagin by *Cunninghamella elegans* out of which 12a -hydroxybufagin and 11a -hydroxybufagin were the new products. Tetracycline residues cause adverse effect on cardiovascular, developmental and metabolic processes and also interfere in antioxidant and immune responses (Yang *et al.,* 2020). Shang *et al.,* 2016 studied bioconversion of commercial tetracycline into seco-cyclines by using *Paecilomyces sp.* (CMB-MF010) which were resistant to fungal enzymatic degradation. Munoz *et al.*, 2020 reported removal of Ampicillin biotransformation from activated sludge by oxidizing ammonium to nitrate using nitrifying consortium.Tadic *et al.*, 2020 elucidated biotransformation pathway of quinolone antibiotic olfoxancin in *Lettuce sativa* L. which led to discovery of 5 new metabolites namely

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OFL279, OFL348, OFL364, OFL376, and OFL378 with potential residual antimicrobial activity.

Biotransformation for conversion of bound compounds into free forms:

Martins *et al.,* 2016 studied enzymatic biotransformation on Red grape pomace (RGP), White Grape Pomace (WGP) and Mixed Grape Pomace (MGP) using enzyme preparations namely tannase alone (T), pectinase plus cellulase (PC) and tannase, pectinase and cellulase (TPC) in which tannase containing preparations were most efficient in increasing total phenolic content in the 3GP samples by releasing gallic acid, caffeic acid, quercetin, and trans-resveratrol. Nakajima *et al.* 2016 reported that free flavonoids content of citrus extracts, increased by biotransformation using *Paecilomyces variotii.*

Conversion of acute compounds to stable compounds:

Rusch *et al.*, 2015 investigated biotransformation of the synthetic antibiotic fluoroquinolone danofloxacin present in liquid manure and faeces of veterinary animals by fungus *Xylaria longipes* into danofloxacin N-oxide which leads to an effective reduction of its antibacterial activity. Likewise, in a study conducted by Pan *et al.*, 2018 determined the conversion of Climbazole (CBZ) into CBZ-alcohol (CBZ-OH) by freshwater microalgae *Scenedesmus obliquus.* Reports indicated thattoxicity of biotransformed product (CBZ-OH) was much lower than that of precursor compound (CBZ).

Leng *et al.,* 2016 studied bioconversion of tetracycline into six biotransformed products with less antibiotic potential by bacterial strain *Stenotrophomonas maltophilia* DT1.During biotransformation N-methyl, carbonyl, and amine groupswere removed sequentially. Hosseini *et al.*, 2020 reported bioconversion of toxic pollutant isobutylraldehyde into highly economic biofuel isobutanol by using genetically engineered bacterial strain *Escherichia coli* XL-1 blue and *E.coli* BW25113.

IV. WASTE WATER MANAGEMENT

It has been reported that biotransformation of macrolide antibiotics (azithromycin, clarithromycin and erythromycin) by an activated sludge culture led to a decrease in residual antibacterial and algal toxicity (Terzic *et al.*2018). In a study conducted by Zumstein and Helbling, 2019 reported biotransformation of antibiotics (Ampicillin, amoxicillin, and daptomycin) by intracellular and extracellular enzymes obtained from wastewater microbial diversity and expressed decreased antibacterial function.

1, 12-Dodecanedioic acid (DDA) is a main compound and an intermediate precursor required for synthesis of perfumes, nylon, lubricants, and cosmetic ingredients (Buathong *et al*., 2019, Buathong *et al*., 2020). Buathong *et al.,* 2020 studied microbial biotransformation of lauric acid from coconut milk wastewater into 1, 12-Dodecanedioic acid (DDA) and 12-hydroxydodecanoic acid (HDDA) by using recombinant yeast *Saccharomyces cerevisiae* expressing gene CYP52A17) from *Candida tropicalis* which functions for oxidation fatty acids to α , ω-Dicarboxylic acids (DCAs).

A dinitrotoulene isomer, 2, 4- dinitrotoluene (2, 4-DNT) is an organic xenobiotic pollutant compound which has carcinogenic and mutagenic effect (Akkaya and Arslam , 2019). Plants, microbes and plant-microbes association has been utilized efficiently for in situ chemical reduction. Microbe associated plant interaction had been found significant in detoxification of pollutants in practical application (Segura and Ramos, 2013, Kiiskila *et al.*, 2015). For example, Akkaya and Arslam, 2019 employed plant- bacterial association for biotransformation of 2,4-DNT by introducing genes required for degradation of 2,4-DNT from *Burkholderia sp*. into *Pseudomonas putida* KT2440 genome and inoculating genetically engineered bacterial strain(KT-DNT) in soil with *Arabidopsis thaliana*.

From past few decades, Hexachlorocyclohexane (HCH) isomers (α-, β-and γ-) have been used as pesticide to prevent vector –borne diseases but due to their adverse effects on environment and human health they were encompassed in persistent organic pollutants(Vijgen et al.,2011 , Kumar and Pannu, 2018). Liu et al., 2020 studied biotransformation of α-hexachlorocyclohexane isomer in wheat (*Quintus*) and identified as 1, 3, 4, 5, 6- pentachlorocyclohexane (PCCH) using compound specific isotope analysis (CSIA) and enantiomer fraction analysis.

Ammonia oxidizing bacteria (AOB) and ammonia oxidizing archaeon (AOA) have been utilized in removal of pharmaceuticals from surface water, waste water and ground water due to non -specific substrate range. (Men et al., 2016). Microorganisms use pharmaceuticals as the only source of carbon through metabolic degradation (Xu *et al.*, 2016).

Men et al.2016, reported biotransformation of a micropollutant ranitidine (RAN) in activated sludge using ammonia oxidizing archaeon (AOA) *Nitrososphaera gargensis* into RAN N-oxide, RAN S-oxide and desmethylranitidine.

Fu *et al*., 2020 studied biotransformation of anti-inflammatory drug diclofenac which has detrimental effect on aquatic life and cyto-toxic effect on human beings, into conjugate metabolites which found to have acute toxic than that of parent compound using aquatic invertebrate species *Hyalella azteca* and *Gammarus pulex*.

Removal of toxic compounds and heavy metals:

Mycotoxins are secondary metabolites produced by fungi of genus Fusarium, *Penicillium* and *Aspergillus* at field and storage levels which may lead to various adverse affects on animals and humans (Loi *et al.*, 2017). For example, Consumption of aflatoxin rich food had shown evidences of immunosuppressive diseases, nutritional deficiencies, lower egg and milk

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production in animals and interaction between diseases like malaria and AIDS /HIV (Gnonlonfin *et al.,* 2013). Chen *et al.,* 2015 studied anaerobic fermentation of aflatoxin B1 and aflatoxin G1 with heat treatment in peanut oil meal by using two strains *Lactobacillus bulgaricus* and *Streptococcus thermophillus*. There was no significant toxicity of AFB1 and AFG1 detected in fermented peanut meal. Furthermore, Zhang *et al*., 2020 reported SSF based biotransformation of aflatoxin B1 into four product named as AFP1, AFP2, AFP3, AFP4 which were lack of lactone ring suggesting minimum toxicity than aflatoxin B1 by using *Lactobacillus helvecticus* FAM22155 and wheat bran as substrate. Moreover Sibaja and his coworkers, 2018 optimized an enzymatic transformation method for biotransforming aflatoxin B1 using different concentrations of enzyme peroxidase at different pH and different temperature which led to efficient reduction of aflatoxin B1 in cow milk and beer.

In a study conducted by Kaewdoung *et al.*, 2016 reported biotransformation of toxic metal compounds (zinc sulfate, copper sulfate, cadmium sulfate, lead nitrate) into their oxalate crystals by selected wood rotting fungi. The selected fungi have been found to be capable of converting zinc sulfate into zinc oxalate dihydrate, copper sulfate into copper oxalate hydrate cadmium sulfate into cadmium oxalate trihydrate and lead nitrate into lead oxalate.

Gupta and Nirwan, 2014 evaluated microbial biotransformation of mercury using heavy metal tolerant Alcaligenesbacterial strain JS-1 isolated from industrial effluent into Mercurous chloride (calomel) which is water insoluble and can be easily separated.

Arsenic exhibits adverse effect on human health and environment. It may lead too genetic toxicity, immune toxicity, biochemical and cellular toxicity, developmental and reproductive toxicity and carcinogenic effect (Matta and Gjyli, 2016). Zhao *et al.*, 2019 reported accumulation and biotransformation of arsenate (As (V)) into arsenite (As (III)) using aquatic plant *Hydrilla verticillata* (waterthyme).

Similarly, Mohd *et al.*, 2019 studied microbial biotransformation of arsenic into insoluble arsenic nanoparticles (AsNP) with reduced toxicity to soil living microbes and plant by using Aspergillus *flavus* (MTCC 25041) isolated from rizhosphere of rice. Yang *et al.*, 2020 studied bioconversion of a polycyclic aromatic hydrocarbon, pyrene from artificially contaminated soil into protocatechuic acid using amalgamation between earthworm (*Eisenia fetida*) and some soil microorganisms.

Medical application:

In recent years, biotransformation technique has been used for identification, production and optimization of bioactive compound in drug discovery (Liu et al., 2010). In vivo biotransformation has shown significant biological activity than that of in vitro evidence. For example, a compound salicin obtained from willow bark has been deglycosylated in colon by intestinal micro-flora and converted to salicylic acid by oxidation reaction in liver (Butterweck and Nahrstedt, 2012).

Moreover, Peeters et al., 2020 studied in vitro hepatic biotransformation of medicagenic acid using human S9 fraction and human liver microsomes which can lead to reduction in in-vitro experiments. Furthermore, Peeters and his coworkers (2020) characterized and elucidated metabolic profile of in –vitro gastrointestinal and hepatic microbial biotransformed products of a *Herniaria hirsuta* using metabolic data analysis method.

In 2019, Magro *et al.* employed solid state fermentation for biotransformation of phenolics in lentil extracts for increasing their antioxidant and antidiabetic activity using fungal strains *Aspergillus oryzae* LBA01 and *Aspergillus niger* LBA02.

Kang *et al.,* 2019 reported bioconversion of saponins and platycosides from *Platycodon grandiforum* root extract by the activity of recombinant E.coli expressing β-glucosiase from *Dictyoglomus turgidum*. The enzyme converted platycosides [platycoside E (PE), platycodin D_3 (PD_3) and platycodin D (PD)] into deglucosylated platycodin D (deglu PD) which showed more anti-inflammatory activity than that of PE, PD_3 and PD.

In a study conducted by Kwon *et al.,* 2018, reported the microbial transformation of isoflavones (genistein and daidzein) from *Pueraria lobata* extract into dihyrogenistein and dihydroaizein respectively with increased anti-melanogenic activity by using *Lactobacillus rhamnosus* vitaP1 strain isolated from human fecal specimen.

Cyclocanthogenol (CCG) is the main cycloartane-type sapogenol found in Astragalus genus which has great value in traditional Chinese medicines because of its telomere elongation, telomerase activation, anti –oxidative and anti- inflammatory properties. (Yu *et al.,* 2018). Ekiz *et al.,* 2018 investigated the microbial biotransformation of sapogenin cyclocanthogenol into 8 unreported metabolites by using endophytic fungus *Alternaria eureka* 1E1BL1 isolated from *Astragalus angustifolius.* (-)-Hinokonin is a lignan lactone which has been found to have anti-leukemic, antiviral, antimicrobial, anti-inflammatory and anti-chagasic activity (Zhou *et al.*, 2015). Arruda *et al.*, 2018 reported fungal biotransformation of (-)-cubebin by Aspergillus *terreus* and *Aspergillus niger into* (-)-hinokinin and (-)-parabenzlactone which showed positive effect against oral pathogen *streptococcus sanguinis.*Rupasinghe *et al.*, 2020 found that biotransformation of cranberry proanthocyanidins to probiotic metabolites by *Lactobacillus rhamnosus* enhances their anticancer activity in vitro in HepG2 cells. Moreover, Bier *et al.*, 2019 determined that biotransformation using solid state fermentation increased antioxidant potential of orange waste by *Diaporthe sp.*

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Biotransformation can be used to produce potent anti-cancer compound like cholchinoside from cholchisine which is a non- heterocyclic alkaloid. In recent year cholchinoside has gained significant important in cancer therapy and anti-tumoral activity (Capistrano *et al.*, 2016, Capistrano *et al.*, 2016). Zarev *et al.*, 2019 demonstrated the capacity of *Astragalus vesicarius* culture to produce cholchinoside by glycosylation of cholchisine from *Glorisa superba* seeds as substrate.

Phenolic compounds have chemo-preventive, anti-allergic and organoleptic effects but they can have harmful effects on the environment if they are available in excessive quantity (Costa *et al.,* 2015). Paz *et al.,* 2019 utilized *Bacillus aryabhattai* BA03 for bioconversion of isoeugenol, ferulic acid and p-coumaric acid into vanillin, 4-vinylphenol and 4- vinylguaiacol with simultaneous production of laccases (Lac) and lignin peroxidases (Lip) which could be collected and reused.

Naturally occurring steroids have been used to produce pharmaceuticals and preparation of creams, sprays, inhalers and drops due to anti-inflammatory, immunosuppressive, sedative, progestational, tyrosinase inhibitory and hormonal properties (Sultana N., 2018).

Recently for the first time, Zoghi *et al.*, 2019 discovered new metabolite i. e. 14α-hydroxyprogesterone by biotransformation of progesterone using *Circinella musae* whichcan be used for preparation of medicines for cardiac patients. Furthermore, Salter *et al*., 2018 performed screening and characterization of microbes which can be used as micro-bioreactor for production of target drug metabolites. It has been reported that water extracts of *Angelica dahurica* root (ADR) after probiotic biotransformation exhibited the most favorable physiological characteristics viz. the antioxidant activity, phenolic content, phenolic composition and anti-tyrosinase activity(Wang *et al.*,2017) It has been reported that biotransformation using *Bacillus safensis* lead to rapid conversion of polydatin to resveratrol (Hu *et al.*,2019).

Table 1: Examples of different types of Biotransformation

Mode of biotransformation	**Source**	**Application of biotransformation**	**Reference**
Fermentation	Local soybean seeds	Increase in antioxidant activity	Sanjukta *et al.*,2015
Enzymatic biotransformation	Brazilian citrus residue	Increase in flavanone production	Madeira Jr. and Macedo,2015
Lactic acid bacteria fermentation	*Myrtus communis* L. (Berries)	Enhancement in antioxidant activity	Curiel *et al.*,2015
Solid state fermentation/ Liquid state fermentation	*Phaseolus vulgaris* (seeds)	Increase in antihypertensive activity and antioxidant activity	Limon *et al.*,2015
Enzymatic fermentation	Citrus juice by product	Increase in flavonoids (hesperetin and naringenin) concentration	Ruviaro *et al.*,2018
Probiotic fermentation	Angelica dahurica root (ADR) extract	Increase in tyrosinase inhibitory and antioxidant activity	Wang *et al.*,2017
Soild state fermentation	Soyabean okara	Improvement of nutritional quality and increase in antioxidant activity	Santos *et al.*,2018
Probiotic fermentation	*Ipomoea batatas* L.(Sweet potato)	Enhancement in nutritional profile and anti-cancer activity	Shen *et al.*,2018
Soilid state fermentation	*Lens culinaris* L.(Lentils)	Increase in antioxidant and anti-diabetic potentials	Margo *et al.*,2019

Table 2: Microbial biotransformation employed for obtaining valuable bioactive molecules

Microorganism	**Substrate**	**Mode of biotransformation**	**Reference**
Lactobacillus plantarum CIR1	Tannic acid	Submerged fermentation	Aguilar-Zarate *et al.*,2014
Recombinant E.coli expressing β-glucosiase from *Dictyoglomus turgidum*.	platycoside E (PE), platycodin D_3 (PD_3) and platycodin D (PD)	Enzymatic transformation	Kang *et al.*, 2019
Penicillium crustosum AN3 KJ820682	Pinus(Pine needles)	Solid State Fermentation	Thakur and Nath 2017b
Dikaryotic strain DK3174 and	Rice and sunflower side streams	Solid state fermentation	Pinela *et al.*,2020

ISSN: 2583-4053
Volume-1 Issue-2 || June 2022 || PP. 68-82
https://doi.org/10.55544/jrasb.1.2.8

monokaryotic strain MK P6 of *Pleurotus sapidus*			
Bacillus subtilis AM1	Tannic acid	Submerged fermentation	Zarate *et al.*,2015
Aspergillus oryzae DAR 3699, *A. oryzae* RIB 40, *Trichoderma reesei* RUT C30	Red grape marc	Solid state fermentation	Zepf and Jin , *2013*

Microorganism	**Targeted compound**	**Biotransformed product**	**Reference**
*Bacillussafensis*SMS1003	Eugenol	Vanillin	Singh *et al.*,2018
Bacterial strain isolated from *Ferula galbanum* soil	β-pinene	α- pinene	Kashi *et al.*,2007
*Bacillussafensis*BS-7	Ferulic acid	Vanillin	Chen *etal.*,2016
Escherichia coli BL21	Taxifolin	Astilbin	Thuan *et al.*,2017
Aspergillus alliaceus	mulin-11,13-dien-20-oic acid	mulin-11,13-dien-16,20-dioic acidand 7a,13b-dihydroxy-mulin-11-en-20-oic acid	Herrera-Canche *et al.*,2019
Bacillus safensis CGMCC 13129	Polydatin	Resveratrol	Hu *et al.*,2019
Aspergillus flavus	Artemisinin	14-hydroxydeoxyartemisinin	Ponnapalli *et al.*,2018
Sphingobium sp.	R-(+)-limonene	R-(+)- α-terpineol	Molina *et al.*,2019
Aspergillus niger	Artemisinin	Artemisinin G	Zhan et al.,2015
Aspergillus flavus (MTCC 9167)	Artemisinin	Artemisinin G	Ponnapalli *et al.*,2018
Aspergillus flavus (MTCC 9167)	Artemisinin	Deoxyartemisinin	Srivastava *et al.*,2009
Penicilliumsimplicissimum	Artemisinin	9α-hydroxyartemisinin	Goswami *et al.*,2010
R. stolonifer	Artemisinin	1α-hydroxyartemisinin	Gaur et al.,2014
Streptomyces griseus (ATCC 13273)	Artemisinin	9-artemisitone	Liu et al.,2006
N. coralline	Artemisinin	Deoxyartemisinin	Ponnapalli et al.,2018
Engineered *Escherichia .coli*	Ferulic acid	Vanillin	Chakraborty et al.,2016
Recombinant *Pediococcus acidilactici* BD16 (fcs +/ech +)	Ferulic acid	Vanillin	Chakraborty et al.,2017
Wickerhamomyces anomalus	(*Z*)-3-Hexenol	(*Z*)-3-Hexenol	Forti et al.,2018
Yarrowia lipolytica	Ricinoleic acid	γ-Decalactone	Braga and Belo,2014
Lactobacillus plantarum KCCM 11613P	Ginsenoside Rb2 and Rb3	Ginsenoside Rd	Jung *et al.*,2017
Mycobacteriumsp. PYR1001	Decursin	Decursinol	Kim *et al.*,2010

Table 3: Plant mediated biotransformation

Plant	**Compound biotransformed**	**Reference**
Wheat(*Quintus*)	α-hexachlorocyclohexane isomer	Liu *et al.*,2020
Zingiber officinale and citrus reticulate	indan -1-one	Bennamane *et al.*,2018
Polygonum multiflorum Thunb	*Furannoligularenone*	*Yan et al.,2008*
Carrot (*Daucus carota*)	Indanol , fluorenol and their analogs	Nagaki *et al.*, 2019
Daucus carota L. (carrot)	4R)-(–)-carvone and (4S)-(+)-carvone	Maczka *et al.*,2018
Vigna radiate	Hydroquinone	Tofighi *et al.*,2016

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ISSN: 2583-4053
Volume-1 Issue-2 || June 2022 || PP. 68-82
https://doi.org/10.55544/jrasb.1.2.8

Phytolacca americana	Daidzein	Fujitaka *et al.*,2017
Levisticum officinale	Geraniol	Nunes *et al.*,2009

V. RECENT ADVANCEMENT IN BIOTRANSFORMATION

Recently, Sharma and Bhardwaj, 2019 produced bacterial nanocellulose (BNC) by fermenting black tea broth prepared using fresh tea leaves with the help of symbiotic consortium of *Acetobacter xylinum* NCIM 2526 and yeast which has greater application in green chemistry, food industry, medical sciences etc. due to its properties like high- water absorbing capacity, mechanical strength and high purity. Furthermore, Martínez *et al.,* 2020 conducted an experiment to determine the conversion of sodium selenite (toxic) into Se-nanoparticles (SeNPs) and Se-amino acids (non-toxic) using 96 selective lactic acid bacteria isolated from wild fruits and flowers. Out of 96 strains eight strains showed significance potential for conversion of inorganic Se into inorganic form.Panic et al., 2020 reported that NADES can be utilized for plant mediated stereoselective biotransformation as they show characteristics such as, non-flammability, low- toxicity, non- volatility. Since last decades, NADES has been used as biocatalyst to minimize challenging procedures in biotransformation. Ma̧czka et al, 2019 demonstrated stereoselective biotransformation of racemic mixture of Indan-1-One and Indan-1-ol by biooxidation and bioreduction using 9 vegetables and 2 fruit as a biocatalyst. During experiment within 24 hours best result for reduction of indan-1-one into S-(+)-indanol was shown by *Daucus carota* L. (carrot), *Petroselinum crispum* L. (parsley) and *Apium graveolens* L. (celery) but at lower yield up to 8%. After 48 hours significant result was shown for oxidation of indan-1-ol into indan-1-one by up to 99% by *Helianthus tuberosus* L. (Jerusalem artichoke).

VI. CONCLUSION & FUTURE LINE OF WORK

As evident from various literature studies, biotransformation emerges as a potent alternative to chemical transformation, being risk prone and costly. Biotransformation, a noble process utilizing various biological systems can be used to modulate and enhancement of bioactive compounds in an environment promising way. Biotransformation has been assumed to play a key role in green chemistry in future because of its sustainable approach. Various fields have demonstrated the potent use of biotransformation for producing tailored and efficient products. In near future, various biotransformation methods can be utilized to improve drug efficacy and to produce nobel drugs that can cure deadly diseases. Recently, area such as, lignin bioconversion to tailored products have gained momentum and attracted increasing attention recently. Research in this field is needed to increase the cost effectiveness of the bioconversion process. A rise in the awareness for ecofriendly methods and pollution control has motivated researchers for bioremediation of petroleum. Major concern these days is the contamination of the environment from petroleum industries. Bioremediation using microbes can be an efficient and fruitful line of work owing to the properties of being cost effective and it also leads to complete mineralization of the contaminants. Microbial biotransformation can also be used for the conversion of steroids to specific compounds which tend to be impossible by traditional methods. Convergence of biology and chemistry has enabled a plethora of industrial opportunities to be targeted. Research on the use of engineered biocatalysts can be used in a varied field of sciences and industries. Research in the fields of biotransformation has entered to an exciting phase. Moreover it can be utilized in future to change the toxicity status of various compounds in an environmentally favorable way. It has got tremendous opportunities in the field of healthcare, agriculture, food industry etc. but transforming compounds using biological entity may pose some pros and cons. Exploration and improvement in analytical techniques suggest that many more developments will be forthcoming. So, plenty future researches are needed to evaluate the cons inspite of posing potential and eco-friendly benefits.

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