



## Biotransformation of phytochemicals: Way forward to gut microbial, nutraceuticals and herbal therapeutics advancements

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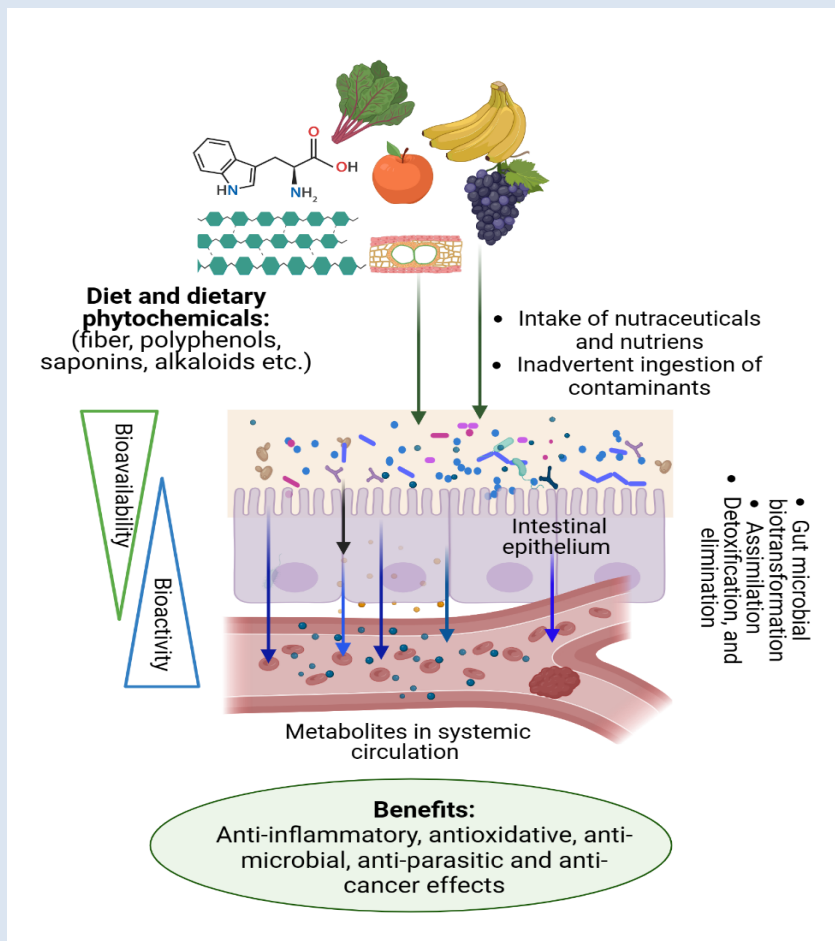
### ABSTRACT

Mammalian gastrointestinal tract is inhabited by trillions of symbiotic microbiotas representing viruses, bacteria, archaea and eukaryotes including yeasts, fungi and protozoa. Compared to humans, the herbivores harbor a complex and metabolically efficient microbes which not only detoxify inadvertently consumed anti-nutritional phytochemicals, but also convert ingested tannin-polyphenols, saponins, phytoestrogens and alkaloids into metabolites which are more available and bioactive than their precursors. Some microbes detoxify toxicants and eliminate them from body. The resulting metabolites display a range of nutritional and therapeutic benefits besides their direct impact on enhancing diversity and functioning of the gut microbiome. Metabolically active gut microbiota and the metabolites generated might be the futuristic alternative biotherapeutics to develop nutraceuticals and plant-based health formulations primarily for 'metabotype 0' individuals. Further insights into novel microbial species, modes of microbial biotransformation of phytochemicals and botanicals will pave the way to develop futuristic non-antibiotic interventions to avert infections and boost human and veterinary health.

**Key words:** Gut microbiome; Phytochemicals; Biotransformation; Biotherapeutics

**Highlights:**

- Gut microbes and dietary phytochemicals prevent host against chronic diseases and infections.
- Little is known about metabolism and modes of action of the GI metabolites of botanicals and herbal supplements.
- Gut microbial metabolites having anti-inflammatory, anti-oxidative and anti-carcinogenic properties might be the futuristic therapeutics.



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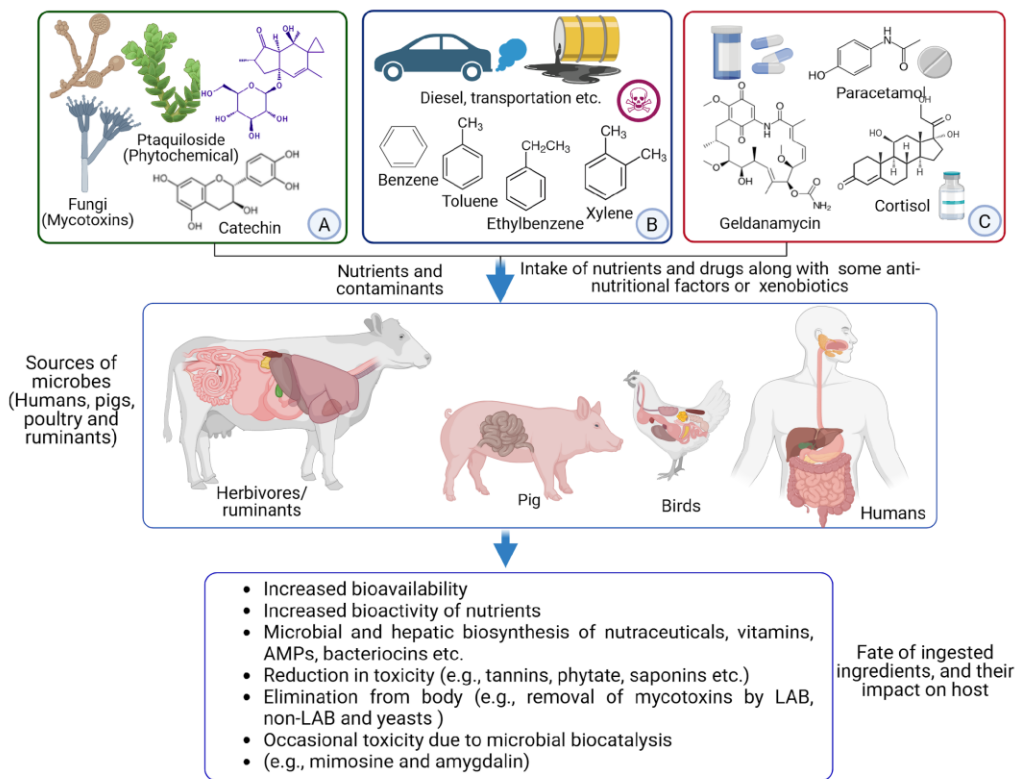
**INTRODUCTION**

Unlike humans and animals, the plants are devoid of movable cellular and humoral immune system, hence depend on innate mechanisms i.e., physical barriers and phytochemicals resulting from primary and secondary metabolism [1]. Indeed, phytochemicals help the plants to ward off phytophagy, predation and cope with pathogens, grazing animals, competitor plants, biotic and

abiotic stresses. During their passage through GI tract, the dietary components undergo physical, biochemical and microbial and hosts’ biocatalytic processes. Microorganisms and their enzymes present in intestinal tract act upon the dietary components and affect their size, molecular structure, bioavailability and activities *in vivo*. Phytochemicals and the resulting metabolites interact with cellular and molecular biological routes,

cellular multiplication, genomic replication, transcription, translation, metabolism, assorted signaling pathway cascades and energy metabolism (Figure 1). Plants, crops, vegetables, pulses, nuts and seeds are the prime sources of polysaccharides (cellulose, hemicellulose, pectin and starch), and phytochemicals like polyphenolic tannins, saponins, terpenoids, alkaloids and flavonoids etc. [2-3]. Therefore, phytochemicals are of interest to human and veterinary nutritionists, botanists and microbial biotechnologists. Indeed, alterations in phytochemicals' bioactivities are attributed primarily to the gut microbial biocatalytic actions, thus

underscores the significance of gut microbiota in digestion, and biotransformation of dietary components, herbal supplements and drugs. Methodically proficient intestinal and exogenously supplemented specialized microorganisms alter the properties of dietary components, health benefits from them, hence can boost benefits from raw ingredients which will benefit the persons categorized as 'metabotype 0' individuals. Overall, it is of top importance to develop evidence-based data for qualitative production and bio-efficacy of functional foods as it is the long standing legacy of Functional Food Center [4-7].



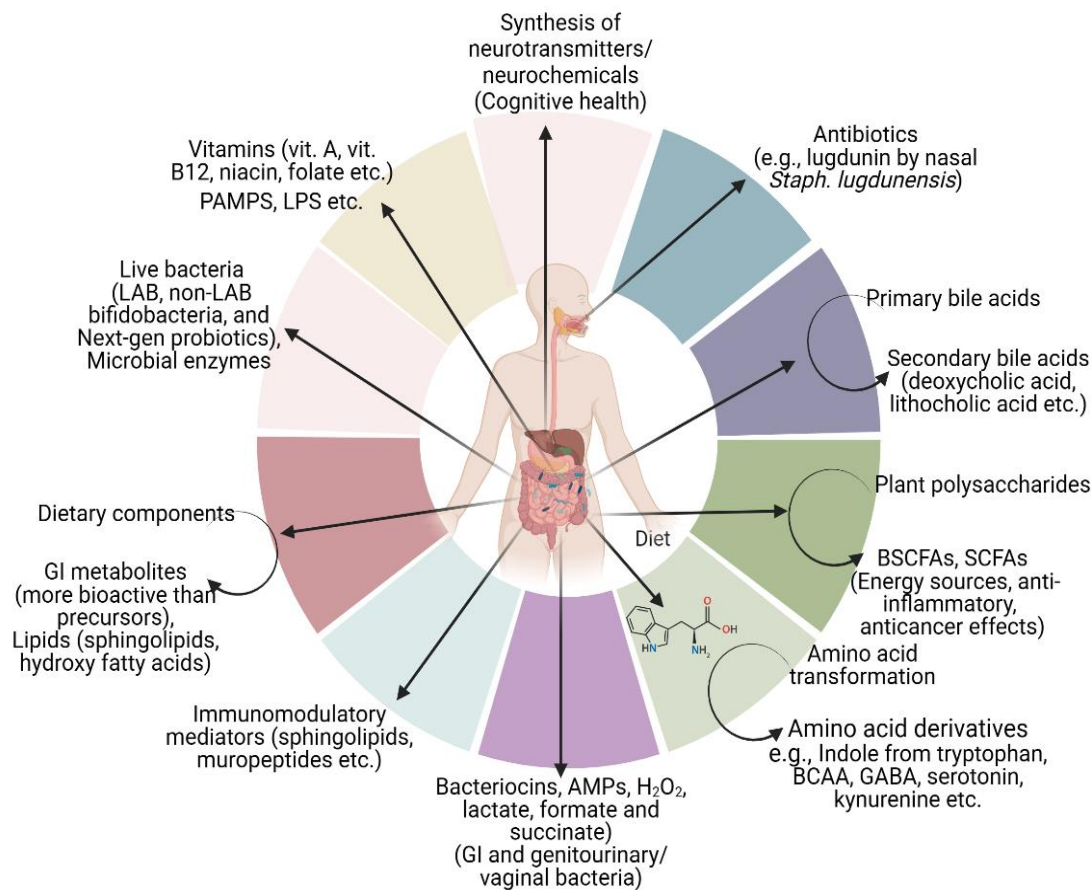
**Figure 1.** Interaction and microbial biotransformation of some harmful chemicals and phytochemicals. GI microorganisms and host enzymes may enhance or reduce bioactivities of the ingested ingredients. Compared to monogastric species (e.g., humans, pigs and birds), the herbivores' gut microbiota has strong metabolic activities. A- agricultural by-products, mycotoxins and agrochemicals; B- xenobiotics from petrochemicals released during transportation; and C-xenobiotics from pharmaceutical industry

**Gut microbial diversity and activities:** The dwelling symbionts are indispensable to host. Herbivores depend

solely on their gut microbes for nutrition and utilization of plant biomass consisting of high fiber and associated

phytochemicals which are toxic when taken in excess. As producers of potentially industrially useful enzymes *viz.*, cellulases, pectinases, proteases, xylanases, phytases and tannases, several microorganisms have been reported from herbivores [8-9]. Similarly, human gut microbiota is a key player in digestive processes, detoxification or removal of anti-nutritional factors taken inadvertently with diet. Besides, GI microbes synthesize antimicrobial peptides (AMPs), types of bacteriocins, organic acids,

primarily the short chain fatty acids (SCFAs), lipids, vitamins and amino acid metabolites possessing immunomodulatory, signal transducing and neurotransmission properties (Figure 2). Microorganisms in GI tract of herbivores are more powerful in terms of saccharolytic activities, production of SCFAs and oligosaccharides biosynthesis of microbial proteins from sources which are not utilized by humans and monogastric species.



**Figure 2.** Gut microbial activities which lead to formation of a number of metabolites with diverse metabolic, physiological and biomedical effects. In addition, the microorganisms found in respiratory tract and women genitourinary tract are prominent sources of AMPs, antibiotics and bacteriocins.

**Abbreviations:** AMPs- antimicrobial proteins, BCAA- branched chain amino acids; BSCFAs- branched short chain fatty acids; GABA-  $\gamma$ -aminobutyric acid; LPS- lipopolysaccharides; PAMPS- pathogen-associated molecular patterns; SCFAs- short chain fatty acids;

**Phytochemicals as therapeutics:** Trees, plants and herbs are inexhaustible sources of raw materials for ethno medicine for millennia as well as commercial production of modern era therapeutics. Phytochemicals which range from simpler alkaloids to highly complex phytosterols

and polyphenolic tannins have variable biological properties and effects on health of an organism [10-11]. The general modes or mechanisms of plant-polyphenols action include binding with proteins and form insoluble tannin-protein complexes, disruption of host cell membrane, inhibition of uptake of nutrients into circulatory system, interruption of cell signaling processes, and obstruction of metabolism and endocrinological processes [12-13].

Depending on molecular organization and conformation, polymerization, and the associated functional moieties, the phytochemicals exhibit different activities viz., anti-oxidative, anti-inflammatory, antimicrobial and anticancer [14-15], and prevention of metabolic disorders [16-17]. For instance, black raspberries, pomegranates and nuts containing high polyphenols, anthocyanin and vitamins have high anti-inflammatory, anti-tumor and anti-cancer activities [18].

**Gut biotransformation of dietary components:** Humans and animals have coevolved with microorganisms, also called as normal microflora which possess remarkable genetic and metabolic proficiencies. Dietary components are acted upon and transformed by microbial enzymatic activities during passage through alimentary canal. Hence, intestinal microorganisms and their metabolic pathways and enzymes are of substantial importance to microbial ecologists, nutritionists and industrial microbiologists [19-20].

Sometimes, humans and animals may inadvertently consume toxicants including industrial chemicals and agrochemicals, also termed as xenobiotics through water and improperly preserved or contaminated foods. Mycotoxins and phytotoxins consumed through

contaminated foods, milk, meat and eggs pose serious health threats. However, toxicity caused depends on several factors including types of toxicants, dose, GI detoxification and riddance from body. Intestinal and general probiotics- the bifidobacteria and lactic acidbacteria (LAB) eliminate certain mycotoxins and degrade phytotoxins, hence serve to alleviate the toxicity [21-22].

**Degradation and utilization of dietary polysaccharides:**

Plant polysaccharides and non-digestible carbohydrates viz., cellulose, hemicellulose, and pectin), resistant starch, indigestible oligosaccharides such as fructo-oligosaccharides non-digestible oligosaccharides like xylo-oligosaccharides, milk galacto-oligosaccharides are components of humans diets. These dietary components are metabolized with the help of bacteria, fungi and protozoa present in distal end of intestine. In humans and other monogastric species including carnivores, the minority of anaerobic bacteria, few fungi and protozoa in large intestine are key microorganisms to utilize dietary fiber [23-24].

Oligosaccharides act as prebiotics to boost intestinal bacteria and introduced probiotics activities. In humans and other monogastric species including carnivores, the minority of anaerobic bacteria, few fungi and protozoa in large intestine utilize dietary plant polysaccharides and oligosaccharides [23-24]. Moreover, the age-related changes of gastric mucosa, its intrinsic factor and acid-peptic activity modification may represent further para-physiological interfering factors [25]. Peptides and SCFAs produced by intestinal bacteria interact with multiple enzymes and target cellular proliferation, epigenetic modification, angiogenesis and

carcinogenesis [26-27], and improve intestinal barrier [28]. Gut microbial metabolites including SCFAs, peptides, urolithins saponins and alkaloid metabolites are absorbed into systemic circulation and distributed to various tissues and organs. They interact with multiple key targets in cellular metabolic pathways that regulate cell proliferation, apoptosis, angiogenesis and metastasis, and contribute to prevent genotoxicity and ensuing colon cancer [26-27]. Of note, *Clostridium* cluster of phylum Firmicutes belonging to genera *Anaerobutyricum*, *Anaerostipes*, *Coproccoccus*, *Eubacterium*, *Faecalibacterium*, *Roseburia* and *Subdoligranulum* metabolize dietary carbohydrates via butyryl-Co-A:Acetate CoA-transferase metabolic pathway and butyrate kinase terminal biocatalysis to synthesize butyrate [27]. Some amino acids are also metabolized in intestine to generate neuro-signaling molecules.

The metabolites of dietary compounds are absorbed into systemic circulation and affect the enzymes involved in epigenetic gene regulation, such as DNA methyltransferases, histone acetyltransferases, deacetylases and demethylases or may alter expression of microRNAs [29]. Intestinal butyrate is a multipurpose bioactive metabolite which is used to generate energy by colonocytes, stabilize-hypoxia-inducible factors that promote anaerobic milieu in intestine, regulate Claudin-1 and synaptopodin genes that maintain gut barrier. In addition, butyrate suppresses pro-inflammatory cytokines (IL-6 and IL-12), and oncogenic Akt/ERK, Wnt, and TGF- $\beta$  signal transduction pathways [27]. Butyrogenic *Roseburia* spp. produce precursors of linoleic acid, and shikimic acid. The shikimate has anti-carcinogenic effects in addition to regulation of NF-

kB/MAPK pathways and control of ulcerative colitis [27, 30].

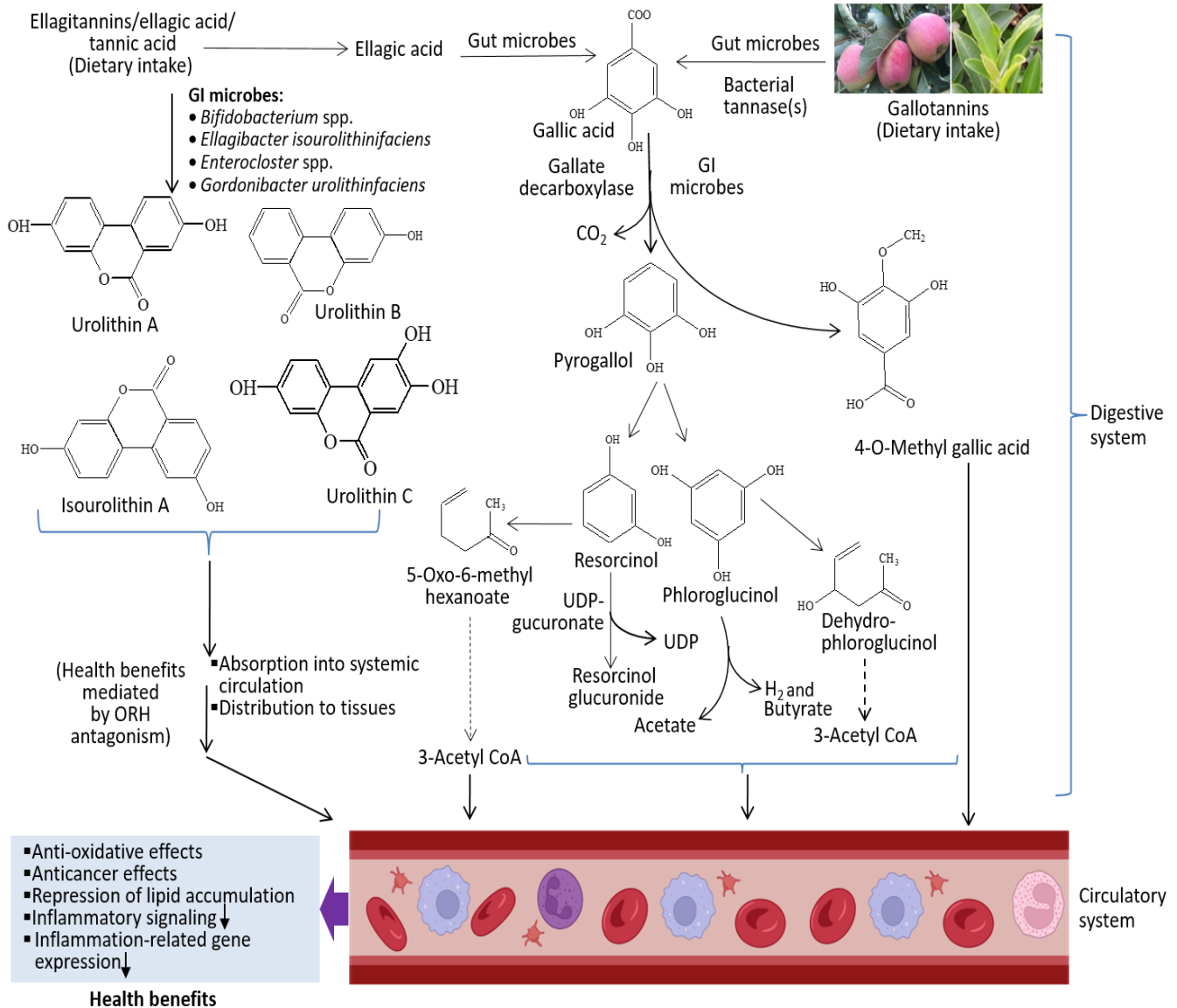
#### DEGRADATION OF PHYTOCHEMICALS:

**Tannin-polyphenols:** Tannin-polyphenols are among most abundant water-soluble polymeric metabolites with tendency to react with proteins and form insoluble tannin-protein complexes. Tannins are divided into two broad classes namely hydrolysable tannins (HTs) (gallotannins and ellagitannins) and condensed tannins (CTs) or proanthocyanidins (PAs).

HTs or pyrogallol-type tannins are polyesters of  $\alpha$ -glucose at the centre and gallic acid and ellagitannins attached to sugars, which on heating with HCl or H<sub>2</sub>SO<sub>4</sub>, yield organic acids i.e., gallic acid and/or ellagic acid. Several plants including medicinal plants (e.g., *Terminalia chebula*, *Phyllanthus emblica*, *Syzygium aromaticum* and *Castanea sativa*), oaks (*Quercus robur*, *Q. leucotrichophora*, *Q. petaea*, *Q. incana*), and gall nuts (*Quercus infectoria*) contain HTs.

On contrary, CTs are the polymers of flavans and contain no sugar moiety. When depolymerized under oxidative milieu, they yield anthocyanidins, hence called as proanthocyanidins.

CTs are extensively studied plant metabolites with reference to their physiological and nutritional effects in humans. Size and molecular structures of tannin-polyphenols determine their bioactivities, degradation in GI tract, and the metabolites generated (Figure 3). Due to their physiological, nutritional and pro-health attributes, CTs are most widely studied tannins [31]. However, size and molecular structure, intake, metabolism (Figure 3) and absorption into systemic circulation account for their bioactivities.



**Figure 3.** Metabolism of polyphenolic tannins and ellagitannins and generation of metabolites such as ellagic acid (EA) and urolithins. The metabolites are absorbed into circulatory system and exercise their effects.

Intestinal and colonic bacteria metabolize tannins and generate metabolites known as urolithins. Urolithin A and urolithin B (hydroxyl-6H-dibenzo[b-d]pyran-6-one derivatives) have anti-carcinogenic effects [32], and act as antagonists of aryl hydrocarbon receptors [33]. Other microbial metabolites such as entrolignans and equol also have anti-cancer and anti-proliferative effects.

Human fecal bacteria, namely *Gordonibacter urolithinifaciens* and *Gordonibacter pamelaiae* belonging to *Eqgethellaceae* family transform ellagic acid into urolithins and isourilithin A under anaerobic conditions [34]. Above strains have therapeutic importance as they can improve health benefits in ‘metabotype 0’ persons upon consumption of foods containing ellagitannins [34].



Naturally existing microbial strains producing urolithins with anti-inflammatory, anti-carcinogenic and cardioprotective properties underscore the importance of human microbiota as probiotics and for commercial production of nutraceuticals and therapeutics [35-36].

**Saponins:** Saponins are detergent-like, triterpene glycosides, bitter tasting natural organic constituents of different medicinal, food crops and toxic plants. When shaken with water, the saponins form a stable foam and lyse red blood cells. Saponins have antimicrobial, anti-protozoa, anticancer and medicinal effects. Several legumes and spices contain multiple bioactive compounds including saponins, alkaloids and phytoestrogens [37]. Thus, saponins present in medicinal plants are widely studied for their metabolism and therapeutic effects. *Panax ginseng* and *Panax notoginseng* saponins (PNS) are widely studied saponins with reference to their therapeutic benefits and molecular biological mechanisms involved.

Ginseng has better cardioprotective, neuroprotective anticancer and anti-diabetic effects. Notoginseng is more effective in cerebrovascular diseases. Hence, it is necessary to unravel the metabolism and pharmacological activities of saponins and their interaction with the host.

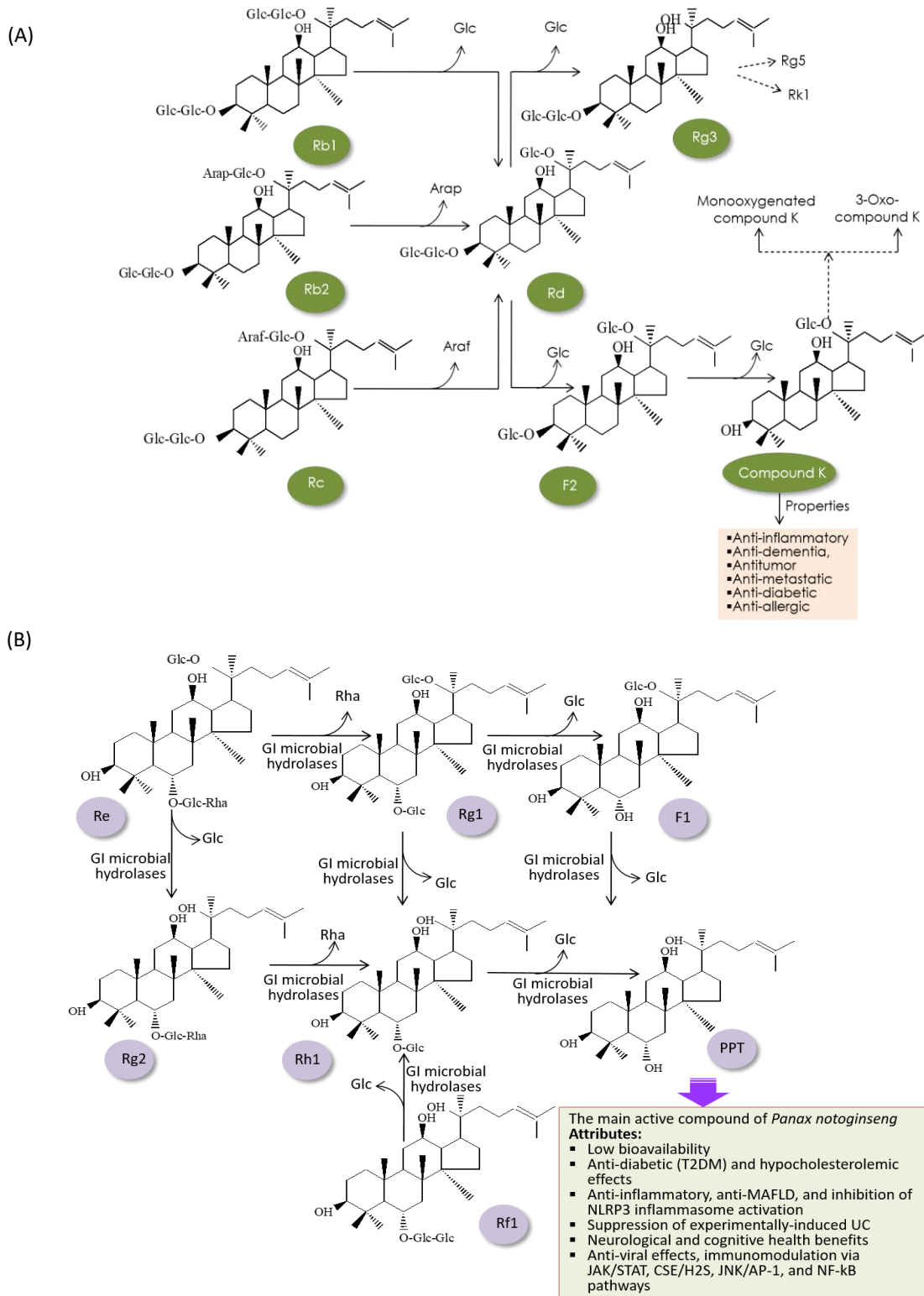
PNS are transformed to different forms including ginsenoside F1 (GF1), ginsenoside RG2 and ginsenoside compound K (GSK). The GSK is functional component of ginseng ginsenosides, and has various clinical applications including cartilage repair, alleviation of osteoarthritis [38-40], anti-inflammatory effects through

inhibition of IL-10, IL-8 and IL- $\beta$  [41], lowering of neuronal damage [42], and promotion of skin health [43].

Mice intestinal bacteria were found to transform American ginseng (*Panax quinquefolius* L) ginsenosides to GSK (20-O- $\beta$ -(D-glucopyranosyl)-20(S)-protopanaxadiol) and ginsenoside Rg3. The study reveals the magnitude of intestinal microbiota in American ginseng-mediated treatment of colitis. Mice intestinal microbes transformed American ginseng saponins to Rb1 and GSK which significantly attenuated experimentally-induced colitis and associated symptoms i.e., abdominal pain, inflammation and pro-inflammatory cytokines levels *in vivo* in treatment group [44]. GSK was more effective against experimentally induced colitis [44].

Human and murine gut LAB and non-LAB such as bifidobacteria, *Bacteroides thetaiotamicron*, and *Streptococcus thermophilus* produce glycosidases such as  $\beta$ -D-glucosidase,  $\alpha$ -L-rhamnosidase and  $\beta$ -D-xylosidase needed for deglycosylation of ginsenosides and synthesis of GSK [45-46]. Notably, enzymes and the procedural steps to prepare final compounds from ginsenosides are not equally efficient. Hence, emphasis is on increasing GSK synthesis by microorganisms [46-47]. Due to diverse therapeutic properties, the current emphasis is on increasing synthesis of GSK through chemical and biochemical approaches. In addition to intestinal microbial deglycolases, lactases, cellulases and  $\beta$ -glucosidases from *Aspergillus niger*, *Aspergillus oryzae*, *Penicillium spp.*, and *Sulfolobus acidocaldarius* are also used to increase synthesis of GSK from concerned precursors [45]





**Figure 4.** Intestinal metabolism of PPD type (A), and PPT type (B) *Panax ginseng* ginsenosides and generation of metabolites which are more active. Microbial metabolic pathways viz., deglycosylation and dehydration are observed for PPD-type ginseng saponins [19]. The PPD and PPT types have different sugar moieties at C-3/C-6 and C-20 in the aglycon. Compared to PPT group, PPD group triterpenoids are easily metabolized by the gut microbiota [16-17, 48-49].

**Estrogenic phytochemicals:** Estrogenic phytochemicals, also known as phytoestrogens, are polyphenolic phytochemicals which have structural homology with human estrogens. Phytoestrogens are abundant in legumes such as subterranean clover (*Trifolium subterranean*), red clover (*Trifolium pratense*) and alfalfa (*Medicago sativa*) and fenugreek (*Trigonella foenum-graecum* L.), lentils, peas, beans and pulses such chick pea (*Cicer arietinum* L.).

There are multiple mechanisms by which phytoestrogens interact with humans and affect physiology. Due to their structural similarity to endogenous estrogens, the phytoestrogens interact with nuclear estrogen receptors, estrogen receptor  $\beta$  (ESR2), estrogen-related receptor  $\gamma$  (GPER1), oxytocin receptor (OXTR), prolactin receptor (PRLR), and various other enzymes involved in synthesis of sex hormones *in vivo* [37].

Phytoestrogens and estrogenic isoflavones such as genistein improve gut metabolism, increase enteric microbial SCFAs [50], and prevent osteoporosis through regulating bone metabolism, reduce bone resorption, maintain bone density and prevent differentiation of osteoblasts [51]. Soy and soy products, and plants belonging to family Fabaceae are important components of human diet, and contain isoflavones. In legumes, the isoflavones exist as *O*-glycosylated, *C*-glycosylated or methylated forms. Glycosylated and methylated isoflavones are more hydrophobic, have high molecular weight, but are less estrogenic than respective precursors. They are poorly absorbed from intestine [52]. Enzymatic microbial conversion of isoflavones by intestinal LAB and bifidobacteria make them more active and absorbable [53-54]. Intestinal biotransformation of isoflavones is essential due to anticancer, cardioprotective and anti-cancer properties of the

metabolites generated [50, 55-56]. *Adlercreutzia equolifaciens* [57-59], *Asaccharobacter celatus* [60-61], *Slackia isoflavoniconvertens* [62], and *Slackia equolifaciens* [63] produce equol from daidzein. Intestinal *Adlercreutzia equolifaciens*, *Asaccharobacter celatus*, *Enterorhabdus mucosicola*, *Slackia isoflavoniconvertens*, and *Slackia equolifaciens* produce equol isomers, the terminal metabolites of daidzein. *Slackia isoflavoniconvertens* produces 5-hydroxyequol and 5-hydroxy-dehydroequol from isoflavone genistein [62, 64]. Equol, resveratrol and urolithins have anti-neuroinflammatory and anticancer effects [65-66], hence have clinical and commercial applications.

Microbial modification of isoflavones is essential as the metabolites generated are more bioactive and confer protection against chronic diseases such as cancer, osteoporosis, CVDs, and menopause [67]. Preliminary *in vitro* studies based on murine microglial cells indicate that equol possesses anti-neuroinflammatory effects, and therefore can have clinical role in neurodegenerative diseases. Three types of neuronal cells viz., microglia (BV-2), astrocytes (C6), and neurons (N2a), were used to evaluate the neurological benefits of the equol. The equol was found to inhibit lipopolysaccharide (LPS)-induced TLR4 activation, mitogen-activated protein kinase (MAPK) activation, NF- $\kappa$ B-mediated transcription of inflammatory mediators, production of nitric oxide (NO), release of prostaglandin E2 (PGE-2), secretion of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), in LPS-activated microglia cells [68]. Isoflavones, ellagitannins and lignans metabolites have multiple clinical benefits such as protection from metabolic diseases and cancer. Therefore, intestinal bacteria which generate bioactive aglycones of isoflavones (daidzein,

genistein and glycitein) present in leguminous foods are of high interest [53-54, 69].

**Alkaloids:** Alkaloids are the naturally synthesized phytochemicals in several genera and species of plants used as medicine and herbs [70]. Morphine, piperine, quinidine, psilocin, cocaine and nicotine are prominent alkaloids in commonly encountered medicinal plants. Berberine (BBR) found in *Berberis* spp., *Coptis chinensis*, and *Hydrastis canadensis* is an alkaloid with diverse health implications.

BBR exhibits notable health benefits by acting at cellular and molecular levels *in vivo* [70-72, 73], or modulates the intestinal microbiota to induce benefits in atherosclerosis [74]. Notably, absorption of ingested alkaloids into systemic circulation depends on their

solubility in aqueous solutions or water. BBR absorption across intestinal epithelium is low due to its poor solubility in water. Intestinal *Enterobacter cloacae* and *Enterobacter faecium* are found to metabolize BBR to dihydroberberine (dhBBR), hence increase its absorption from intestinal lumen [75]. Studies from *in vitro* and model animals have shown that microbial metabolites of BBR confer health benefits including anticancer [3, 76], antidiabetic effects (anti-T2DM) through protection of pancreatic  $\beta$ -cells, increasing tissue sensitivity to insulin via GLUT-1, GLUT-4 and insulin type 1 (Ins-1) receptor activity [77], ameliorate colitis symptoms prevent inflammatory responses by strengthening intestinal barrier [78-80]. BBR and its microbial metabolites are potential modulators of intestinal microorganisms which confer multiple health benefits [81-83] (Table 1).

**Table 1.** Biotransformation of some phytochemicals during passage through gastrointestinal tract

<b>Phytometabolites</b>	<b>Microbial species</b>	<b>Recommendation and inferences (references)</b>
<b>A. Tannin-polyphenols</b>		
Ellagitannins <i>(Combretum aculeatum)</i>	Mixed gut microbes <i>Ellagibacter isourilithifaciens</i>	Synthesis and urolithin (D) 7-mediated antagonism against mycobacteria [94] Transformation of ellagitannins and EA into isourilithin A [95]
EGCG	<i>Lactobacillus fermentum</i>	EGCG along with <i>L. fermentum</i> confers second generation synbiotic effect, anti-oxidative effects and modulation of immunity [96]
Catechins	<i>Eggerthella lenta</i> <i>Flavonifractor plautii</i>	Transformation of catechins and epicatechins to 5-(3,4-dihydroxyphenyl)- $\gamma$ -valerolactone and 4-hydroxy-5-(3,4-dihydroxyphenyl) valeric acid [97]
Urolithins		Dose-dependent activity of urolithin A and B, weaker estrogenic and strong anti-estrogenic activities [32]
Urolithins (Uro-A, Uro-B, Uro-C and Uro-D)		Urolithin-mediated inhibition of cell proliferation and cell-cycle progression at S and G2/M phases. Urolithin A was most effective [98]
Ellagic acid	<i>Bifidobacterium pseudocatenulatum</i>	Transformation of EA to urolithins A and B [99]
	<i>Ellagibacter isourolithinifaciens</i>	Formation of isourolithin A from EA [95]
	<i>Gordonibacter</i> sp. Multiple human gut	More than one strains are involved in production

<b>Phytometabolites</b>	<b>Microbial species</b>	<b>Recommendation and inferences (references)</b>
	strains ( <i>Eggerthellaceae</i> family)	of urolithin from EA [100] Complete conversion of EA into isourolithin-A [34]
	<i>Enterocloster bolteae</i> DSM 15670 (Human-origin)	Formation of urolithins (Uro-A and Uro-B from Uro-C and IsoUro-A, respectively), hence might have applications to produce functional foods, beverages and nutraceuticals [101]
Quercetin	<i>Bacteroides fragilis</i> , <i>Clostridium perfringens</i> <i>Eubacterium ramulus</i> , <i>Lactobacillus</i> spp. <i>Streptococcus</i> spp.	Transformation of quercetin to metabolites with altered bioavailability and therapeutic properties [102]
<b>B. Estrogenic phytochemicals</b>		
Phytoestrogens (genistein, daidzein, resveratol, enterolactone)	Colonic microbes	Anti-proliferative activities, microbial metabolites found to be potential endocrine-disrupting molecules [32]
Isoflavones	Mixed human gut microflora	Gut microbial transformation of phytoestrogens to O-desmethylangolensin, equol, urolithins and enterolactones [103]
	<i>Leuconostoc citreum</i> (Recombinant strain)	Bioconversion of isoflavon glycosides into aglycons having more activity [104]
	<i>Slackia equolifaciens</i> (Human intestine)	Production of equol from isoflavones [63]
	<i>Limosilactobacillus mucosae</i> INIA P508 and Bifidobacteria	Bioconversion of isoflavones and formation of soy beverages containing bioactive aglycones daidzein and genistein [105]
Formononetin, Biochanin A	LAB, bifidobacteria	Transformation of formononetin and biochanin A into daidzein, and genistein [106]
Daidzein, and Daidzin and trans-polydatin	<i>Slackia isoflavoniconvertens</i> (Human intestine) <i>Bifidobacterium breve</i> MTCC1274	Formation of equol, and 5-hydroxy-equol from genistein and daidzein [107-108] <i>B. breve</i> MCC1274 promotes bioavailability of daidzein in the gut, improves absorption of isoflavones [109]
Daidzein	<i>Enterococcus faecalis</i> <i>Lactobacillus rhamnosus</i>	Transformation of daidzein [54]
Daidzein and chungkookjang (Fermented soy)	<i>Lactobacillus intestinalis</i>	<i>L. intestinalis</i> -mediated efficient production of equol from daidzein and chungkookjang [67]
<b>C. Saponins</b>		
<i>Penax notoginseng</i>	Mixed gut microflora	Transformation of PNS into GF1, GRH2, GSK and saponins (PNS) and PPT [12]
<i>P. ginseng</i>	Mixed rat gut microflora	Formation of seven ginsenosides (ginsenosides Rg1, Re, Rf, Rb1, Rc, Rb2, and Rd), deglycosylated metabolites of K and Rh1, showing a differential

<b>Phytometabolites</b>	<b>Microbial species</b>	<b>Recommendation and inferences (references)</b>
		pattern of metabolism of saponins [48]
PD-type <i>P.ginseng</i>	<i>Bifidobacterium lactis</i> <i>L. rhamnosus</i> HN001	Differential transformation ginsenosides. <i>L. rhamnosus</i> transformed Rb1, Rc, and Rb2 into Rd. <i>Bifidobacterium lactis</i> transformed ginsenosides Rb1, Rc and Rb2 to Rd [110]
American ginseng compounds	Human gut microbiota	GSK and Rg3 found to be major metabolites, attenuation of colitis, abdominal pain and gut inflammation. GSK had high anti-inflammatory effects [56]
Ginsenosides (Rb1 and F2)	Recombinant <i>Escherichia coli</i> ( <i>Bgy2</i> genes from <i>L. brevis</i> )	Transformation of Rb1 and F2 into Rd and GSK [111]
	Recombinant <i>Escherichia coli</i> BL21(DE3) ( $\beta$ -glucosidase from <i>Flavobacterium johnsoniae</i> )	Optimization of conditions, and bioconversion of ginsenoside Rb1 and gypenoside XVII into ginsenosides Rd and F2 by recombinant bacterium [112]
<b>D. Alkaloids</b>		
Berberine	Mixed gut microbiota	Modulation of gut <i>Akkermansia</i> spp., anti-atherosclerotic and therapeutic effects [81]
	Mixed gut microbiota	Reduction in gut clostridia and their BSH activity, accumulation of TCA (Tian et al., 2019), activation of gut butyrogenic activities [71-72]
Morphine (MO) model	Mixed gut microbiota	The study describes the negative consequences associated with use of opioids [113]
MO, and MO-GSH adduct	Mixed intestinal microbes	Anaerobic conversion of MO and MO-GSH into [114]
<b>E. Dietary fiber (plant polysaccharides)</b>		
Plant polysaccharides	Multiple bacteria (e.g., butyrogenic bacteria, <i>Faecalibacterium</i> , lactobacilli, and <i>Roseburea</i> )	Multiple health benefits including regulation of immune system, anticancer [115-118], prevention of metabolic disorders [119-120], strengthening of intestinal barrier, and prevention of damage to intestinal barrier [121-122], regulation of energy metabolism

**Abbreviations:** BSH- bile salt hydrolase; DHMO- dihydromorphine; EA- ellagic acid; EGCG; GSK- ginsenoside compound K; MO-Morphine; MO-GSH- morphine glutathions; PNS- Penax ginseng saponins; PPT- protopanaxatriol; TCA- taurocholic acid

14 weeks feeding of 0.5g/litre of BBR to Apoe<sup>-/-</sup> mice led to substantial increase in intestinal *Akkermansia muciniphila*, and reduced endotoxemia induced by fat-enriched diets [81]. BBR reduces load and severity of intestinal colorectal tumorigenesis and cancer. Studies have shown that BBR modulates intestinal bacteria,

alleviates intestinal SCFAs *viz.*, butyrate, acetate and propionate levels, upregulates occludin and ZO-1, and reduce fecal LPS load and colitis-associated CRC tumorigenesis [84]. The study concludes that BBR might be used as a novel approach and experimental basis to treat colitis-associated cancer CAC in clinical practices.

#### **Improving biotransformation and delivery of microbial**

**metabolites:** Phytochemicals, herbal beverages and drugs undergo metabolism in intestine and generate intermediates that are critically important to host. It implies that microorganisms are important to enhance bioavailability of raw plant ingredients. Poor aqueous stability, low absorption and the microbial efficiency to convert phytochemicals are major impediments in the use of nutrients and herbal ingredients. However, all individuals are not equally efficient to utilize phytochemicals and dietary nutrients. The persons who lack specific intestinal microorganisms fail to generate specific metabolites. The individuals are called as 'metabotype 0'. For instance, synthesis of equol from isoflavones is observed in 30-50% of human populations [85]. Alternative approaches such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, liquid crystals and microemulsions are suggested to increase the stability and delivery of biotherapeutics.

Bioengineering and genome-editing are the methods to enhance metabolic capacities of selected strains of microorganisms [86-87]. Recombinant *Escherichia coli* expressing daidzein reductase, dihydrodaidzein reductase, tetrahydrodaidzein reductase, and dihydrodaidzein racemase from human intestinal *Slackia isoflavoniconvertens*, enhanced (-)-5-hydroxy-equol and 5-hydroxy-dehydroequol from isoflavone genistein [64].

Similarly, *Escherichia coli* expressing  $\beta$ -glucosidase of *Bifidobacterium breve* ATCC15700 enhanced synthesis of GSK from ginsenoside F2, and was used for its

commercial scale production [16-17]. Phytochemicals, for example, coloring agents, pigments, flavor agents, antioxidants, binders texturing agents are extensively used in food industry. Phytochemicals with anti-oxidative properties have applications in functional foods. Metabolic engineering has made possible the large scale production of botanicals and phytochemicals from inexpensive and recyclable effective sources [88].

#### **OUTLOOK AND CHALLENGES**

Microorganisms and their genes have emerged as a new frontier to understand the molecular biological basis of traditional medicines. Gut microbiota that activate or mediate transformation of ingested phytochemicals, herbal formulations or ethnomedicine should be investigated for use as novel probiotics and drug-delivery vehicles. Herbivorous ungulates yield bacteria and fungi with multiple metabolic properties [89-91]. Although such bacteria and fungi may not be used as food supplements in humans, these microbial strains can be used to prepare products at commercial scale.

Intestinal microorganisms and their metabolic efficacies are the emerging frontiers to understand interaction of nutraceuticals and herbal medicine with host and host microbiota. Microorganisms that activate, transform and improve bio-availability of nutraceuticals in herbal therapies or ethnomedicine could be the promising microbial additives or drug-delivery vehicles for 'metabotype 0' individuals as well as for commercial production of particular compounds. Selected microorganisms can be engineered or edited to enhance biotransformation of phytochemicals whose utilization is inefficient *in vivo*.

Certain phytochemicals may have adverse effects *in vivo*. For instance, opioid alkaloids, morphine and their pharmacological derivatives may have adverse impact on gut-barrier, and cause inflammatory responses.  $\beta$ -glycosidases of intestinal bacteroidetes, Firmicutes and

Actinobacteria breakdown amygdalin and release toxic HCN [92]. Nonetheless, the amount of HCN generated, half-life and absorption from intestinal surface are too less to cause toxicity [92]. Similarly, the non-protein amino acid, named as mimosine, present in certain protein-enriched forage plants such as *Leucaena leucocephala* (Lam.) de Wit (family Fabaceae) is converted by microbial enzymes to more toxic metabolites, namely 3,4-DHP and 2,3, DHP [93]. The microorganisms which promote availability and therapeutic efficiency of metabolites are the futuristic novel probiotics. Because inferences obtained about above therapeutic benefits of the herbal components and their metabolites are from model animals, their efficacy should be tested cautiously in humans.

Despite constraints, there is increasing demand for functional foods owing to their proposed and claimed health benefits. Importantly, the dietary components affect composition and functioning of gut microbiota, and consequently the host health. Therefore, herbal formulations should be selected cautiously and as per standard guidelines, especially in health-conscious consumers (Martirosyan, 2023)

## CONCLUSION

Lower intestinal tract is important organ for transformation of miscellaneous dietary elements and drugs and utilization of dietary polysaccharides, and transformation of nutrients. Intestinal bacteria modulate physiological processes such as enzyme activity, redox potential redox potential and signalling transduction by means of metabolites generated for dietary carbohydrates, amino acids and fats pathways. In addition, GI microbiota are crucial to degrade the inadvertently ingested harmful components and eliminate them from body. Several normal bacteria themselves have valuable therapeutic and probiotic properties. This way, the gut bacteria may enhance

remedial benefits of phytochemicals in general by transforming them to metabolites that are biologically simpler and more active *in vivo*. However, thorough studies are necessary to revisit the bacteria and their pro-health attributes inferred from *in silico*, *in vitro* and animal model-based inferences.

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