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Review Article

Exploring Microbial Biotransformation of Electro-Homoeopathic Plant Constituents and Its Relevance to Diabetes Mellitus

Niranjan Ram[1], Monika[2]

[1,2]*HRIT University, Ghaziabad, Uttar Pradesh, India*

[2]*Corresponding Author : dr.monika231988@gmail.com*

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Abstract *- Diabetes mellitus is a complex metabolic condition characterized by insulin resistance, β-cell dysfunction and chronic inflammation and host–microbial interactions. Plant preparations are composed of several phytochemicals that are known to have a wide range of biological effects and bioavailability in the gut, which could significantly be influenced by the gut microbiota. Microorganisms in the intestine have the enzymic capacity to break, hydrogenate, reduce, dehydroxylate, and hydrolyse natural substances, producing metabolites with different characteristics than their parent substances. Electro-Homoeopathy is a system of botanical medicine that uses plant essences in complex medicines, but so far, there is not much information about the microbial biotransformation of the plant matter components of these medicines. A perspective review of potential relationships between microbial degradation of components of Electro-Homeo plants and mechanisms related to diabetes, focusing on the case of Hydrastis canadensis and the component berberine. Conversion of berberine to dihydroberberine by the intestinal bacteria offers a mechanistic rationale. Phenolic compounds, polyphenols, microbial metabolites, short-chain fatty acids, bile acid signalling, intestinal barrier function, inflammation and insulin sensitivity are also taken into account in the review. Currently, there is little evidence indicating that the whole Electro-Homoeopathic formulation has anticariogenic effects mediated by the microbiota. Thus, this association has to be considered as a mechanistic hypothesis that can be tested but not accepted as a therapeutic mechanism. Future research associating formulation identification with LC–HRMS/MS, anaerobic microbial transformation, rapidly needs to be completed, with metagenomics and metabolomics, followed by functional validation, to establish pathways. This approach will move the field forward by experimental testing of relationships between botanical constituents and the diabetes-related biology of gut microbial metabolism. New constituents produced by microbial transformations might change the biological destiny of electrohomoeopathic plant constituents, and the formulation-level antidiabetic activity in these components is not confirmed and should be tested chemically, microbiologically, and metabolomically in addition to being functionally assessed.*

Keywords *- Berberine, Dihydroberberine, Gut microbiota, Insulin resistance, Metabolomics, Short-chain fatty acids.*

1. Introduction

Diabetes mellitus is a common chronic condition throughout the world, much of which is characterised by hyperglycaemia for more than three months from defects in insulin production and/or insulin action. The more typical clinical type of type 2 diabetes is characterized with insulin resistance, declining insulin-producing β-cell function, abnormal regulation of hepatic glucose production and defects in adipase and skeletal-muscle metabolic defects. With the passage of years, diabetes has become more significant and is ongoing to become more severe. The World Health Organization (WHO) estimated that there were 200 million diabetic people in 1990 and 830 million diabetics would be present in 2022. (WHO, 2024)

The search for plant-derived molecules able to regulate glucose metabolism started a long time ago, and modern phytopharmacology showed that there are a multitude of plant-based molecules that have an impact on carbohydrate digestion, insulin signalling, oxidative stress and inflammatory pathways (Grover et al. 2002). The fate of the drug in the body after giving a phytochemical orally is, however, much more complicated than just the content of the parent compound in the plant. Many phenolic acids, flavonoids, glycosides and alkaloids, before entering into the systemic circulation, undergo metabolism; this metabolic process is of particular importance for the gut due to the gut biota (Selma et al. 2009; Braune and Blaut, 2016).

Microbial biotransformation can change the polarity, stability, absorbability in the intestine, affinity of a compound to a receptor and biological activity. Metabolites created by the microbiota are sometimes more absorbable than the original species. The berberine – dihydroberberine pathway is particularly evident: it is converted to dihydroberberine by the intestinal bacteria with much

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greater intestinal absorption, and conversion is reduced when bacteria in the intestine are reduced, resulting in diminished metabolic effects of orally administered berberine (Feng et al. 2015).

In Electro-Homoeopathy, an unusual botanical context in which this principle may be relevant is provided. It is described in exercises that Electro-Homoeopathy is a medical system of medicines involving plants, developed by the historical figure and scientist Dr. Count Cesare Mattei, who uses various plant-derived extracts and "essences" as medicines, which are prepared individually and then mixed in preparation of the remedies. According to a review on the system, there were some 114 species of plant used in various quantities and dilutions in individual instances, and these were processed and recombined in different ways, and they represented 87 families (Sureshbabu et al. 2020). The medicinal plants of the groups Scrofoloso, Canceroso, Angiotico, Linfatico, Vermifugo, White Electricity and Blue Electricity are considered for the preparation of Electro-Homoeopathic medicines, which have been reported to produce good results in lowering glucose by improving insulin sensitivity. Another review on Angiotico-1 revealed *Avena sativa*, *Hydrastis Canadensis* and *Sanguinaria Canadensis* together with *Arnica Montana* and *Capsella Bursa-Pastoris* as other constituent plants (Sabat and Nayak, 2022).

The key thing is that the scientific question is not: is it a fact that Electro-Homoeopathy as a whole has to be assumed to have antidiabetic activity? Instead, what can be asked is if the chemically identifiable constituents of the Electro-Homoeopathic plants can undergo microbiota-dependent transformation, altering their mode of exposure, or biological activity, in pathways in relation to diabetes. It should be clarified here that evidence of an individual phytochemical, evidence of a source plant and evidence of a finished Electro-Homoeopathic formulation are not mutually convertible.

This is a narrative review to merge three sets of literature: one describing the plants utilized as Electro-Homoeopathic sources and their phytochemical profile, two describing the mechanistic studies on microbial metabolism of plant-derived compounds, and three describing literature evidencing gut microbial metabolites and plant-derived metabolite pathways in conjunction with the diabetes pathway.

The review also highlights the places in which evidence is direct, the places in which evidence needs to come from other chemically similar compounds, and the places where dedicated formulation-level experimentation is still needed.

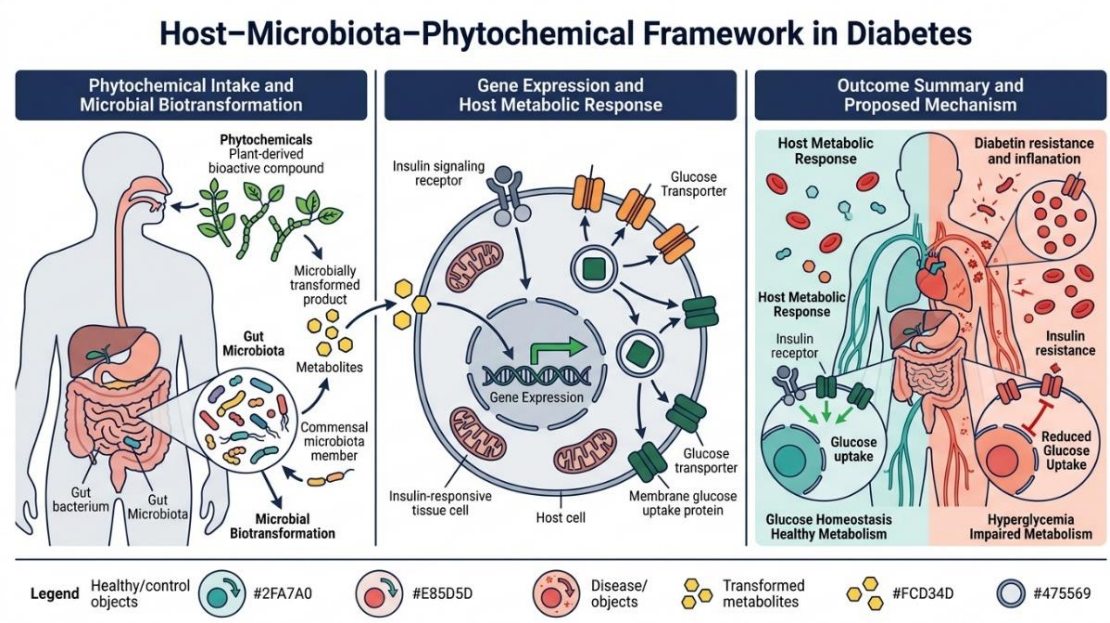


Fig. 1 Proposed host–microbiota–phytochemical framework for Electro-Homoeopathic plant constituents in diabetes

2. Literature Search and Scope

Amongst the literature, the spectrum of Electro-Homoeopathy spans historic descriptions, plant-specific phytochemistry, experimental microbial metabolism, pharmacokinetics, and diabetes biology, with significant differences in study design and end-points, and we have not found a single paper that we felt would sufficiently meet every criterion to be included in a systematic review. The historical background, the preparation methods, the botanical range and pharmacological effects reported in literature were mainly carried out from the literature prepared by the users, who have formed a small library (Sureshbabu et al. 2020; Sabat and Nayak 2022). Further literature research was conducted by PubMed and scholarly databases with various combinations of keywords such as Electro-Homoeopathy, medicinal plants, phytochemicals, gut microbiota, microbial biotransformation, berberine, dihydroberberine, polyphenol metabolism, chlorogenic acid, diabetes, and insulin resistance.

Primary mechanistic studies were prioritized for specific pathways of biotransformation, authoritative reviews for general concepts of phytochemistry and microbiome, and recent literature for the diabetes–microbiota interface. Studies on the Electro-Homoeopathic formulations are limited, and the evidence from other systems of botanical medicine is not considered as evidence of efficacy. Rather, the model is defined by chemically and mechanistically significant findings that are used to test the model.

3. Electro-Homoeopathy as a Botanical and Chemical System

3.1. Historical and Conceptual Background

Electro-Homoeopathy (also called electropathy in some literature) was introduced in Europe during the nineteenth century and came to be linked to Count Cesare Mattei. It is described as a treatment based on plants, in which the remedies are composed of complex formulas that are made of plant essences, instead of a particular purified active molecule.

Count Cesare Mattei states that it is often the proportion of each individual plant essence in the remedy that is varied when creating a remedy for a specific disease and a specific constitutional type. A complex botanical is important to modern pharmacology in that it may have several different chemical components that may interact with one another. If a mixture contains multiple compounds, the biological activity of which cannot be predicted from that of its most familiar marker compound. However, varying its methods can change the profile of chemicals to be administered.

3.2. Spagyric Processing and Implications for Phytochemical Composition

The preparation procedure followed in the production of Electro-Homoeopathic medicines involves the extraction of plant material, elimination of volatile parts, fermentation, rectification, collection of elements of mineral or ash origin and their subsequent combination or cohobation. From a chemical point of view, each stage may affect the molecular form and the quantity of constituents.

Extraction can lead to bringing in either polar or non-polar compounds to the initial fraction, fermentation can lead to biological transformations, distillation can lead to volatiles being concentrated, and subsequent recombination can lead to a matrix of chemically different fractions being created (Sureshbabu et al. 2020). Such a processing history is especially important for an interpretation with a microbiome focus. In the event of fermentation or during other means of manufacture, the plant material delivered to the gastrointestinal tract may be different from the original plant in molecular structure. Thus, it is important for a future study to differentiate three chemical statuses: phytochemical profile of the authenticated plant, the chemical profile of the ready-made Electro-Homoeopathic medicine and metabolite profile after handling the intestinal bacteria of humans.

3.3. Botanical Diversity of Electro-Homoeopathic Preparations

A wide range of botanical materials has been reported in the Electro-Homoeopathic literature. Some 114 species of plants from 87 families have been reported, and a few species of these are commonly available in India. The different plant essences are then re-combined in varying quantities and proportions to make various remedies (Sureshbabu et al. 2020). This diversity results in chemically diversified forms of Electro-Homoeopathy, which is not one drug intervention.

The phytochemistry of five plants described in Angiotico-1 literature is particularly informative as it is explored independently: *Arnica montana*, *Avena sativa*, *Capsella bursa-pastoris*, *Hydrastis canadensis* and *Sanguinaria canadensis* (Sabat and Nayak 2022). These plants belong to several classes of chemical importance, such as sesquiterpene lactones, phenolic amides, flavonoids, phenolic acids and benzophenanthridine alkaloids.

4. Phytochemical Constituents of Selected Electro-Homoeopathic Plants

4.1. Arnica Montana

Arnica montana has been reported as a constituent compound of Angiotico-1 and contains sesquiterpene lactones, including helenalin, dihydrohelenalin derivatives and flavonoids, besides other secondary metabolites (Sabat and Nayak 2022; Kriplani et al. 2017). The sesquiterpene lactones are chemically reactive molecules whose biological activity has been documented, but their enteric microbial metabolism has not been extensively investigated, as in the case of berberine.

Further, experimental metabolism studies show that helenalin-related compounds can be metabolised in a specific way under controlled conditions, consistent with the notion that they should not be ruled out of future metabolite screening experiments, but that these experiments must be conducted in a specific way to exclude the presence of such a gut microbial pathway (Jürgens et al. 2022).

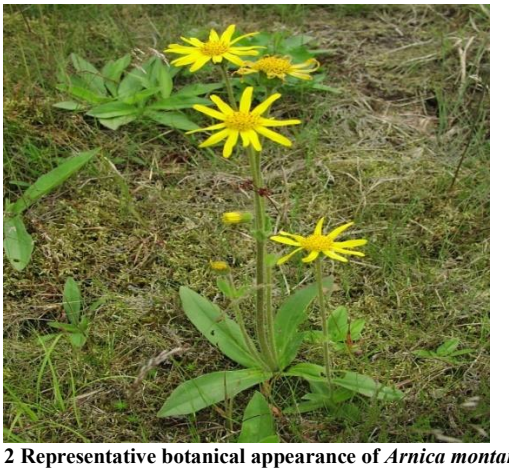


Fig. 2 Representative botanical appearance of *Arnica montana* (Asteraceae

Source: https://en.wikipedia.org/wiki/Arnica_montana

4.2. Avena Sativa

Avena sativa is rich in the phenolic compounds, the β-glucan and other components. The anti-inflammatory and antioxidant activity of Avenanthramides, which are characteristic oat phenolic amides, have been investigated (Chen et al. 2007). The Electro-Homoeopathic literature also has reported observations relating to the glucose-lowering activity of *Avena sativa* in the plant or formulation context in the absence of a demonstrated microbiota-mediated mechanism (Sabat and Nayak, 2022). The impact of Avena extends beyond the fate of the individual avenanthramides, given that some components of other families of aven toads are fermentable by the GIT, which affects the microbiome and plays a role in the production of short-chain fatty acids (Portincasa et al. 2022). Hence, it is important to identify direct microbial transformation of phenolics from indirect effects due to microbial fermentation of the botanical matrix when studying whole Avena preparations.



Fig. 3 Representative botanical appearance of *Avena sativa* (Poaceae)
Source: https://en.wikipedia.org/wiki/Oat

4.3. Capsella Bursa-Pastoris

Capsella Bursa-Pastoris contains flavonoids, phenolic acids and phenol glycosides. Glycosidic bonds have important implications in intestinal biotransformations as intestinal bacteria can cleave glycosidated plant compounds to produce aglycones (Cha et al., 2017). These aglycones can then be metabolized further, resulting in metabolites that are specifically smaller phenols, which might have altered absorption properties.



Fig. 4 Representative botanical appearance of *Capsella bursa-pastoris* (Brassicaceae)
Source: https://en.wikipedia.org/wiki/Capsella_bursa-pastoris

4.4. Hydrastis Canadensis

The greifensprong or waterwort, *Hydrastis canadensis*, is the most significant plant in connection with this mechanistic argument that we developed in this review. The plant is rich in Isoquinoline Alkaloids like Berberine, Hydrastine and Canadine, as well as phenolic components like chlorogenic and related acids (Mandal et al., 2020). Berberine was investigated by itself with respect to its glucose- and lipid-modulating activity, and clinical and experimental literature investigated its potential to be used for metabolic disease (Zhang et al. 2008; Liang et al. 2019). The literature supplied with the medicines given only gives this detail for the Electro-Homoeopathic medicines, and according to it, *Hydrastis canadensis* is a constituent of Angiotico-1, and there are observations on hypoglycaemia with regard to glucose absorption and metabolism that affect insulin sensitivity and secretion (Sabat and Nayak 2022).



Fig. 5 Representative botanical appearance of *Hydrastis canadensis* (Ranunculaceae)
Source: https://en.wikipedia.org/wiki/Goldenseal

4.5. Sanguinaria Canadensis

Sanguinaria Canadensis possesses Benzophenanthridine type alkaloids, specifically Sanguinarine and Chelerythrine, and a group of compounds named protopine type. They exhibit a variety of biological activities, such as antimicrobial and anti-inflammatory, but pharmacologically, they present important safety aspects. The toxicity of Sanguinarines has been reported in the literature and should be taken into account during efficacy and safety assessment in addition to metabolism (Croaker et al. 2016). Although the metabolic conversion of Sanguinarine to Dihydrosanguinarine has been reported, it is not definitely known whether this metabolism is very specific to the intestinal microbiota of humans. The conversion of sanguinarine to dihydrosanguinarine is described, but insufficiently studied, specific to the intestinal microbiota of humans (Dvořák and Šimánek 2007). The Sanguinaria, therefore, should be considered as an informative chemical for future biotransformation studies and not as an established antibiotic agent that is metabolized by microbiota.



Fig. 6 Representative botanical appearance of *Sanguinaria Canadensis* (Papaveraceae)
Source: https://en.wikipedia.org/wiki/Sanguinaria

Table 1. Representative Phytochemical classes in selected electrohomoeopathic plants and their relevance to microbial biotransformation (Sureshbabu et al. 2020; Sabat and Nayak 2022; Kriplani et al. 2017; Jürgens et al. 2022; Mandal et al. 2020; Croaker et al. 2016; Dvořák and Šimánek 2007).

Plant	Representative constituents	Likely/known microbial reaction	Potential metabolite consequence
Arnica montana	Helenalin/dihydrohelenalin esters; flavonoids	Transformation of sesquiterpene lactones is plausible; the gut-specific route is not established.	Potentially altered polarity/reactivity
Avena sativa	Avenanthramides; phenolics; β-glucan	Phenolic metabolism; microbial fermentation of matrix polysaccharides	Smaller phenolics and microbial fermentation products
Capsella bursa-pastoris	Flavonoid glycosides; phenolic acids	Deglycosylation, reduction, ring cleavage	Aglycones and low-molecular-weight phenolics
Hydrastis canadensis	Berberine; hydrastine; canadine; phenolic acids	Nitroreduction of berberine	Dihydroberberine has greater intestinal absorption
Sanguinaria canadensis	Sanguinarine; chelerythrine; protopine	Reductive metabolism; gut contribution unclear	Dihydrosanguinarine and other metabolites

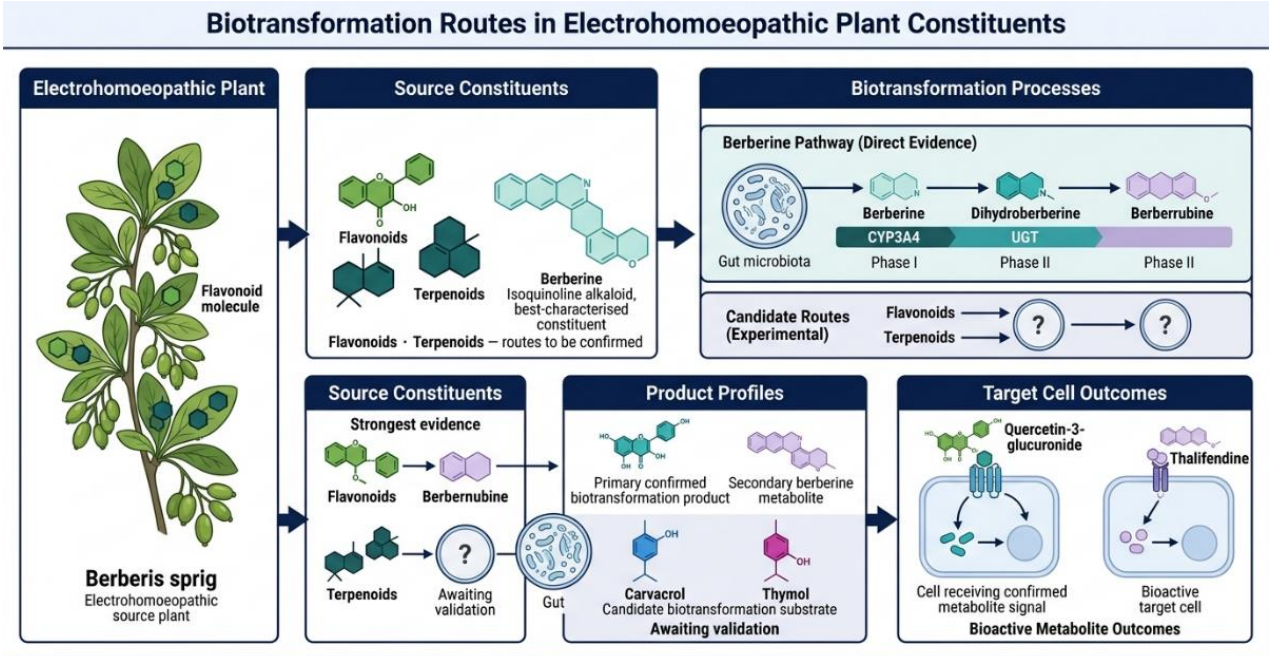


Fig. 7 Representative biotransformation routes relevant to constituents of selected Electro-Homoeopathic plants.

5. MICROBIAL Biotransformation as a Determinant of Phytochemical Fate

5.1. Why the Microbiota Matters for Orally Administered Phytochemicals

The gastrointestinal tract is not simply a passive absorption surface. It is very rich in microbial constituents, and these microbes have the ability to metabolise dietary compounds and xenobiotics in a way that mammalian metabolism may not. In the case of plant-derived molecules, this microbial activity may dictate whether a parent molecule is poorly absorbed or whether it could be converted to an aglycone for subsequent absorption or undergo sequential events that result in smaller metabolites that are able to be absorbed systemically (Selma et al. 2009; Braune and Blaut 2016). The result is very dependent on which compound is involved. An increase in bioavailability, decreased activity, activation of a prodrug-like molecule, detoxification of a reactive molecule or production of a metabolite with a different pharmacologic profile can all be considered microbial reactions. Inter-individual variations in the repertoire of microbial enzymes also imply that exposure to the same dosage of the same phytochemical could lead to differential exposure to the metabolites in different individuals.

5.2. Deglycosylation and Hydrolysis

Generally, Glysosylation increases the polarity of plant metabolites and may affect their uptake. Bacterial β-glucosidases and related glycosidases can break glycosidic bonds, thus releasing aglycones for further microbial reactions (Braune and Blaut 2016; Duda-Chodak et al. 2015). Other major routes of hydrolysis involve ester hydrolysis, especially for phenolic acids like chlorogenic acid.

5.3. Reduction, Hydrogenation and Dehydroxylation

Some reactions, called “reductive reactions”, are especially important to alkaloids and unsaturated phenolic compounds. In the case of microbial nitro-reduction, a direct example is presented in the case of Berberine (Feng et al. 2015; Tomás-Barberán et al. 2014), which is nitro-reduced, and in the case of how chlorogenic acid is metabolized, it undergoes Hydrogenation and Dehydroxylation when incubated with human faecal microbiota. These reactions may significantly change the chemical behaviour and hence have to be considered when predicting the biological activity of plant preparations.

5.4. Aromatic-Ring Cleavage and Generation of Smaller Phenolics

The complex polyphenols can be transformed into lower molecular weight phenolic acids by a series of microbial reactions. Such products can be more readily absorbed than the parent compound, and may be responsible for biological effects systemically (Braune and Blaut 2016; Duda-Chodak et al. 2015). These products vary according to the identity and/or concentration of the substrate and the metabolic state of the microorganism(s) responsible for their production.

5.5. Inter-Individual Variability and Metabotypes

There is no uniformity in microbial metabolism between persons. The chlorogenic-acid faecal microbiota study of humans showed that the sequence and the speed of the turnover of bacteria were different for every donor, but at the same time, the metabolic pathways led towards similar end products (Tomás-Barberán et al. 2014). Donor-dependent patterns are identified as well for other phytochemicals, in addition to providing a mechanistic basis for the concept of metabotypes. This variation might matter for the assessment of complicated plant preparations in diabetes, as the same preparation might create different metabolites in two people.

6. Microbial Biotransformation of Constituents Relevant to Electro-Homoeopathic Plants

6.1. Berberine: the Strongest Mechanistic Precedent

Berberine is a quaternary Isoquinoline Alkaloid found in the leaves of *Hydrastis Canadensis* (aka golden ragwort) and other medicinal plants. The Glucose and Lipid Metabolism of its metabolic activity has also been widely researched (Mandal et al., 2020; Zhang et al., 2008; Liang et al., 2019). The main Pharmacokinetic problem with berberine is that its parent compound is not readily absorbed in the intestine. A mechanism was proposed by Feng et al., which involves enzymes in the human gut, specifically Microbial Nitroreductases, to transform berberine into Dihydroberberine.

The intestinal absorption rate of Dihydroberberine was around 5 times higher than that of Berberine in animal experiments. The native gut bacteria were depleted by antibiotic treatment, the conversion of Berberine to Dihydroberberine was inhibited, the systemic exposure to Berberine was reduced, and the glucose- and lipid-lowering activity of Berberine was reduced in mice (Feng et al., 2015).

This is congruent with the current analysis and supports the correlation of four pieces of evidence: a plant-derived constituent, a well-defined microbial reaction, changed intestinal absorption and a metabolic phenotype. Thus, it provides a scientifically valid explanation for investigations of the possible involvement of the same pathway in the activity of the Electro-Homoeopathic preparations using Hydrastis.

Of course, the size restriction is also important. All collected evidence in the purified form of berberine may not be suitable for use when studying a completed Electro-Homoeopathic formulation. Amount of berberine delivered, presence of coexisting constituents and formulation matrix, as well as the nature of the berberine as a processed ingredient, can affect microbial transformation. Therefore, it is recommended to carry out a direct experiment to compare the concentration of berberine from the plant used as a source, the finished formulation, compared to the concentration of berberine transformed by the microbiota.

6.2. Chlorogenic Acid: A Model for Phenolic-Acid Transformation

Chlorogenic acid metabolism is chemically related and is a relevant model since *Hydrastis Canadensis*, which is the source of the chlorogenic acids, is believed to possess both chlorogenic acid and related phenolic acids (Mandal et al. 2020). Tomás-Barberán et al. found a second pathway by incubating chlorogenic acid with fecal microbiota of nine human donors, where sequential hydrogenation, dehydroxylation and ester hydrolysis occur with different pathways depending on the individual. The reactions coincided with the production of 3-(3-hydroxyphenyl)-propanoic acid, and this compound might be further metabolized in certain donors (Tomás-Barberán et al. 2014). This example is not important because chlorogenic acid metabolism demonstrates an Electro-Homoeopathic effect. Instead, it exemplifies the extensive degree of metabolomic alteration that can be produced by human gut microbiota from a plant phenolic compound, and the variability of metabolites as modified by donor, i.e., microbiome, differences.

6.3. Flavonoid Glycosides and Capsella-Related Constituents

In *Capsella Bursa-Pastoris*, flavonoids and phenolic glycosides have been found, which could make this an attractive plant for microbial Deglycosylation (Sabat and Nayak 2022; Cha et al. 2017). It is generally recognized from literature that Bacterial Glycosidases may release the Aglycones, which may undergo further reduction and ring-strain opening (Braune and Blaut 2016; Duda-Chodak et al. 2015). The metabolites that are formed can markedly differ in absorption and biological activity from the parent glycosides. However, at present, there is no single Capsella-derived metabolite that has been shown to act via gut microbiota to mediate a diabetes-related effect. This is the correct interpretation as one of plausibility in the mechanistic sense. This distinction will guard against the common mistake of assuming a general biochemical reaction to be a therapeutic effect of a disease.

6.4. Avena-Derived Phenolics and the Matrix Effect

Avena Sativa has an Avenanthramide rich component and the Carbohydrate-Rich matrix (including the β-glucan component). Although at least some oat phenolics are systemically available, the Avenanthramides can also be detected following oat consumption (Chen et al. 2007). Meanwhile, Microbial Fermentation of β-Glucans and other Carbohydrates may aid in the intestinal environment and help make short-chain fatty acids (Portincasa et al. 2022). Therefore, future research needs to differentiate between two mechanisms: direct microbial transformation of Avena phenolics and indirect metabolic changes caused by the action of the fermenter on the plant matrix. A formulation-level experiment measuring both the phytochemical metabolites, together with the SCFAs, would be more insightful than one measuring only phytochemical metabolites or SCFAs separately.

6.5. Sanguinaria-Derived Alkaloids: Transformation and Safety

Sangwinaria Canadensis contains biologically active Benzophenanthridine Alkaloids such as Sanguinarine (Croaker et al. 2016). The compound is metabolically transformed to Dihydrosanguinarine, and the role of intestinal microbiota in this transformation is still not well understood (Dvořák and Šimánek 2007). This uncertainty has a scientific significance as the microbiota can detoxify or activate xenobiotics, and Antimicrobial Phytochemicals have the potential to modify the metabolizing Microbiota. Sanguinaria should thus be studied using a multifaceted approach to assessing efficacy and safety. The measurements of parent-compound disappearance and metabolite formation should be carried out simultaneously with the assessment of the microbial composition and its Cytotoxicity. This would not take the premise that the microbial transformation is always good.

Table 2. Evidence hierarchy for microbial transformation of selected constituents

Constituent/Plant	Evidence for microbial transformation	Diabetes relevance	Interpretation
Berberine / *Hydrastis Canadensis*	Direct: Gut Nitroreductases generate Dihydroberberine; Microbiota depletion reduces conversion.	Glucose- and lipid-lowering effects attenuated after depletion	Strongest mechanistic candidate
Chlorogenic Acid / Hydrastis-related Phenolics	Direct in human fecal microbiota; donor-dependent Hydrogenation, Dehydroxylation and Hydrolysis	Phenolic metabolites may have different systemic effects	Strong general precedent; not formulation-specific
Flavonoid Glycosides / Capsella	General Microbial Deglycosylation and Downstream Phenolic Metabolism	Potential effects through altered metabolite exposure	Plausible; direct Capsella–Diabetes link lacking
Avena Phenolics / β-Glucan	Phenolic Bioavailability plus microbial fermentation of fibre	SCFA and Metabolic signalling may contribute	Matrix-dependent; mechanism needs separation
Sanguinarine / Sanguinaria	In vivo reductive metabolism; gut contribution unclear	Primarily pharmacological and safety relevance	Insufficient for antidiabetic inference
Helenalin derivatives / Arnica	Metabolism demonstrated experimentally; gut-specific evidence is limited	No established microbiota-mediated diabetes mechanism	Research candidate

7. Gut Microbiota and Diabetes Mellitus

7.1. Microbial Dysbiosis and Metabolic Dysfunction

Gut microbiota is involved in the processes of nutrient metabolism, in the maintenance of the intestinal barrier, in bile-acid transformation and immunological regulation. The changes in microbial community and its function have been consistently linked to insulin resistance and low-grade chronic inflammation in type 2 diabetes (Zhang et al. 2021; Chen et al. 2026). While the different studies vary in the types of identified taxa, the common mechanistic background is that the metabolites secreted by the microbiomes and/or host–microbe interactions can have a direct impact on the systemic glucose metabolism. This offers valuable background information on phytochemicals. The phytochemical may interact directly with a host target, modify microbes or create a microbial metabolite that is bioactive for diabetes; or interact with all three, directly with the host, in altering the microbes, and in the production of a bioactive metabolite for diabetes.

7.2. Short-Chain Fatty Acids and Glucose Homeostasis

Microbial fermentation of the dietary substrate leads to the production of short-chain fatty acids, especially acetate, propionate and butyrate, which affect intestinal and systemic physiology. They have the ability to activate G-protein-associated receptors, to modulate Enteroendocrine Hormone activities, to regulate epithelial membranes and to reduce the inflammatory signal (Portincasa et al. 2022; Yang et al. 2026). Even if the more prevalent Phytochemicals in the matrix are not converted to circulating antidiabetic metabolites, the composition of a plant matrix can regulate glucose.

7.3. Bile-Acid Signalling and The Gut–Liver Axis

Signalling effect of Gut-Microorganisms on the host through converting primary bile to secondary bile to interact with receptors like Farnesoid x receptor (FXR) and Tgr5. There have been associations between insulin resistance or type-2 diabetes and altered bile-acid metabolism, and the association is reciprocated as bile acids can also affect the microbial ecosystem (Sui et al. 2022). Compounds found in plants could therefore alter microbial metabolism in an indirect way that could affect diabetes via the bile-acid pool.

7.4. Intestinal Barrier and Metabolic Inflammation

Access to microbial products and, consequently, to systemic inflammation is an important aspect of intestinal barrier dysfunction. There is evidence of the role played by butyrate-producing microorganisms and their metabolites in maintaining epithelial homeostasis, and their dysbiosis may lead to increased pro-inflammatory signalling (Portincasa et al. 2022, Cha et al. 2017, Mandal et al. 2020, Zhang et al. 2008, Liang et al. 2019, Croaker et al. 2016, Dvořák and Šimánek 2007, Duda-Chodak et al. 2015, Tomás-Barberán et al. 2014, Zhang et al. 2021, Chen et al. 2026). When a phytochemical changes its form in the body, such as due to a community change, the effect it can have downstream may be on the intestinal inflammation, and it may not directly affect the β-cells of the pancreas.

7.5. Insulin Signalling and Metabolic Tissues

Microbial metabolites can influence processes in the liver, in the skeletal muscle and in adipose tissue, which regulate the uptake and production of glucose. There can be many interacting pathways between insulin sensitivity pathways and other concurrent pathways linked to SCFA, including bile acid receptors and inflammatory mediators (Zhang et al. 2021; Chen et al. 2026). The relevance to Electro-Homoeopathic preparations can best be expressed as a network hypothesis for a plant constituent: a compound can be metabolized by gut microorganisms, the metabolite can have an impact on gut or systemic signaling cascades, and the metabolic phenotype may result from multiple interacting pathways (Yang et al. 2026; Sui et al. 2022).

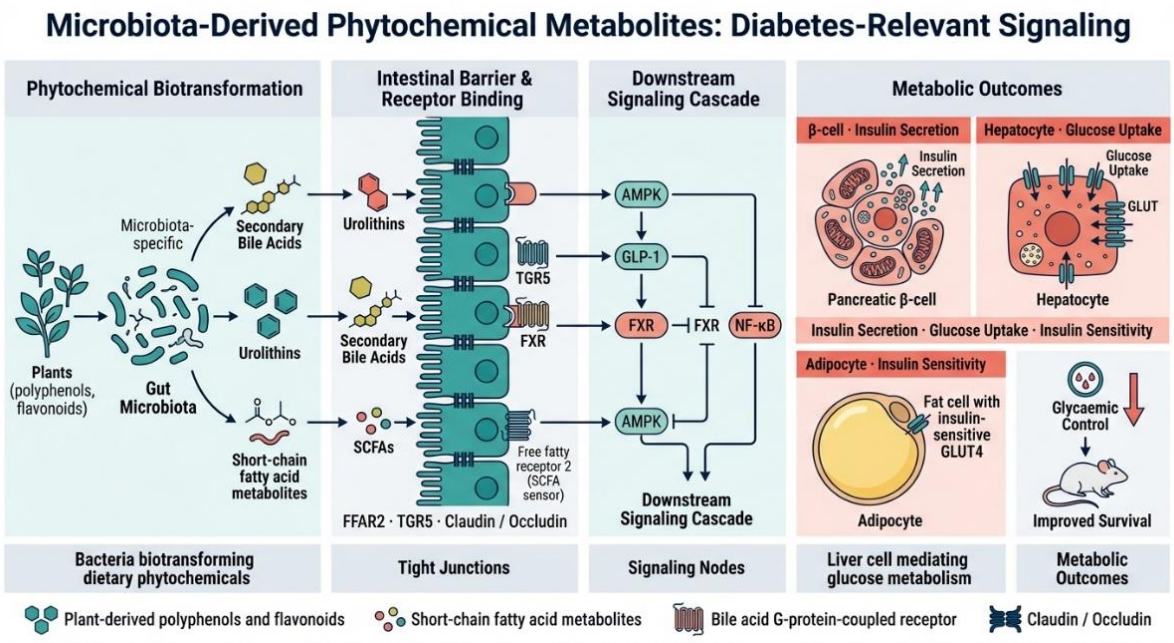


Fig. 8 Potential diabetes-relevant consequences of microbiota-derived phytochemical metabolites

8. Bidirectional Interaction Between Plant Constituents and Gut Microbiota

8.1. Phytochemicals as Microbial Substrates

The simplest interaction is the conversion of substrate to other molecules; microorganisms generate molecules of different chemical structures based on molecules that are derived from plants (Selma et al. 2009; Braune and Blaut 2016). This can be achieved by increases the amount of a compound available for intestinal absorption, as in the case of the berberine pathway (Feng et al. 2015).

8.2. Phytochemicals as Ecological Modulators

The relationship is reciprocated, Bi-Directional. A few plant components also have Antimicrobial or growth-regulating properties. This is especially significant with regard to Hydrastis and Sanguinaria, which contain the active compounds responsible for the antimicrobial properties (Mandal et al. 2020; Croaker et al. 2016). A preparation might thus simultaneously provide a source of microbes to feed on but also be a selective pressure on the community that can metabolize the microbes. This is an issue because it carries implications for microbiome studies. This increase may be due to enrichment of a producer organism, and a decrease may be due to direct inhibition of the organism producing the given metabolite(s). Thus, the composition of the microbiome does not provide a biotransformation mechanism; additional measurements of metabolites and functional enzyme assays are needed.

8.3. Microbial Capacity as a Determinant of Response

The repertoire of Microbial Enzymes is different for each person, which means that two people taking the same plant-based compound can produce different levels of downstream metabolites (Tomás-Barberán et al. 2014). This variability provides a potential rationalization of the differences in response seen with complex botanicals and may warrant considering the possibility of using microbial metabotypes as predictors of response.

8.4. Formulation Matrix Effects

In an Electro-Homoeopathic preparation, he could concentrate a number of preparations of botanical origin in one place, namely, the intestine. Competition, interference, cross-feeding between microbial species and Microbiological Enzyme (Lipase/Esterase) competition can affect the production of metabolites. Such effects cannot be expected to be addressed in experiments with single purified compounds. So, formulation-level experiments should contain both the complete formulation and purified markers.

9. Integrated Mechanistic Model for Electro-Homoeopathic Constituents and Diabetes

There is evidence available to uphold a stepwise model. First, the compounds in the plants undergo changes during the preparation process of Electro-Homoeopathy, and are then delivered as a chemical matrix. Secondly, the Gastrointestinal environment is able to separate compounds by solubility, stability and absorption. Third, the molecules that reach the colon can also undergo further modification by microbial reactions like Hydrolysis and Reduction, Dehydroxylation, and other reactions. Fourth, metabolites can be localized in the lumen of the intestine, bind with receptors of intestinal epithelial cells or to the microflora or be absorbed and taken part in the bloodstream. Lastly, these metabolites may impact pathways that involve glucose homeostasis, inflammation, and the role of the intestinal barrier and the host's energy metabolism. Berberine is the most effective single case. "Several electrolyte-based preparations have been proposed for *Hydrastis Canadensis* – the berberine is one of the most important alkaloids of the herb – and the microorganisms present in the gut convert the berberine to a more readily absorbed form – Dihydroberberine – as shown in ref 5 and ref 13". The below-mentioned metabolic impact of Berberine has been evaluated individually in diabetes (Zhang et al. 2008) and Dyslipidaemia (Liang et al. 2019). This is a coherent mechanistic link, not yet evidence for a clinically relevant antidiabetic effect for an Electro-Homoeopathic formulation of Hydrastis.

The other plants are less well documented. The microbial transformation of Phenolic Glycosides and phenolic acids appears to be universal, but the activities that these metabolites pose to diabetes are not well understood, and a variety of formulation-specific metabolite profiles have appeared (Braune and Blaut 2016; Cha et al. 2017; Tomás-Barberán et al. 2014). In addition, Avena can potentially interact with the microbial fermentation via its carbohydrate matrix, while Sanguinaria can present a more intricate efficacy–toxicity challenge due to its Bioactive Alkaloids (Chen et al. 2007; Croaker et al. 2016).

The integrated model thus consists of two layers. The first is a well-known biochemical layer, in which microorganisms are able to convert plant-derived molecules. The second is a theory of a "hypothesis layer"; those changes might play a role in the metabolic changes that have been observed by Electro-Homoeopathy preparations. It is crucial to retain such distinction for scientific credibility.

Table 3. Proposed mechanistic links between microbial transformation and diabetes

Step	Mechanism	Potential diabetes consequence	Evidence status
1. Chemical exposure	Preparation and digestion determine parent-compound availability	Changes the substrate reaching the intestinal microbiota	Requires formulation-specific chemistry

2. Microbial transformation	Hydrolysis, reduction, dehydroxylation and ring cleavage	Generation of metabolites with altered bioavailability/activity	Well established for multiple phytochemicals
3. Intestinal signalling	Metabolites interact with epithelial and microbial pathways	Barrier integrity, GLP-1 and inflammatory tone	General evidence
4. Systemic exposure	Absorbable metabolites enter circulation	Potential effects on the liver, muscle and adipose tissue	Compound-specific
5. Metabolic phenotype	Changes in glucose handling, inflammation or insulin sensitivity	Potential improvement in glucose homeostasis	Not established for electrohomoeopathic formulations

10. Future Research Perspectives

Future research would first require the authenticating of the Electro-Homoeopathic formulations by means of botanical verification, voucher documentation, and the identification of metabolites by LC–HRMS/MS in anaerobic experiments with the faecal microbiota of various donors, to characterize the processes of conversion of parent-compounds and formation of metabolites. In addition, metagenomic and functional analyses can identify microbial genes and enzymes that catalyse these transformations, and targeted and untargeted metabolomics can be used to help identify bio-active microbial metabolites. The following assays, which diagnose the pathways in diabetes, should then be used for the evaluation: α-glucosidase and DPP-4 inhibition, glucose uptake, AMPK/AKT signalling pathways, oxidative stress, and inflammatory pathways. Finally, the necessary microbiota-transformation to produce the metabolic effects of the original formulation or its microbial metabolites could be established with conventional, microbiota-depleted or gnotobiotic animal models.

11. Conclusion

Pharmacokinetic and biological characteristics of plant material constituents, following oral administration, may be altered by microbial biotransformation. Of the investigated plants, *Hydrastis Canadensis* and Berberine have a better mechanistical explanation, while the remaining plants—*Avena Sativa*, *Capsella Bursa-Pastoris*, *Arnica Montana*, and *Sanguinaria Canadensis*—are good potential candidates for further research. Chemical profiling coupled with microbiota metabolomics, microbial transformation testing, and functional validation studies should be combined in future research to come up with an idea of whether or not the chemicotransformation products of the microbiota play a role in the effects related to diabetes.

Author Contribution Statement

The first author, Niranjan Ram, contributed to the conceptualization of the review, literature search, collection and organization of relevant information, analysis and interpretation of the literature, and preparation of the manuscript. The second author, Monika, provided supervision and scientific guidance, critically reviewed and edited the manuscript, and contributed to its intellectual development and finalization. Both authors reviewed and approved the final version of the manuscript.

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