PHYTOCONSITUTENTS AS BIOENHANCERS: A REVIEW

Abstract

Bio-enhancers are the compounds that enhance the bioavailability of active pharmaceutical ingredients without itself having any pharmacological action. Most of them are of natural origin and do not have any side effects. They enhance the bioavailability by influencing variety of mechanisms involved in the drug action like penetration enhancement, improving metabolism, enzyme inhibition, drug targeting etc. Use of these compounds help to reduce the dose frequency which in turn reduces drug retention in turn causing the toxicity and it also helps in developing cost-effective products. Present days these are widely used to enhance the bioavailability of anti-bacterial, anti-viral, antibiotic, anticancer, anti-inflammatory, cardiovascular drugs etc and effective drug targeting. The present review is designed to emphasize the importance of certain phytoconstituents working as bio-enhancers, their classification and different mechanisms of their activity.

Keywords

Bioenhancer, Bioavailability, drug targeting, Piperine, Quercetin, Curcumin, Emodin.

Introduction

Bio-enhancers are the chemical moieties or majorly phytoconstituents that enhances the plasma concentration and further promote the efficacy of a drug. They don't have any pharmacological activity of their own and get easily eliminated from the body without causing any side effects. They not only increase the bioavailability of active pharmaceutical ingredients like anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, antibiotics, cardiovascular drugs etc. but these can also be used for the effective absorption of nutrients and vitamins. They enhance the bioavailability of drugs using various mechanisms like elevating intestinal absorption, blocking drug metabolising enzymes which further stops liver and intestinal degradation, as well as blocking efflux mechanisms resulting in the blockage of drug elimination by gut as illustrated in the figure: 01.

There are number of benefits illustrating the benefits of using bioenhancers, including reduction in quantity of dose intake due to enhanced plasma drug concentration, cost reduction due to lower intake of drug, lesser side effects due to lower usage of drug, increased drug tolerance leading to reduction in drug resistance. Better biocompatibility, safety and economy due to their natural origin (1, 2, 3, 4).

Bio-enhancers classification

Based up on the origin of the bioenhancers, these may be classified as of plant origin and animal origin as stated in the table 1:

Table 1: Bioenhancers and their origin

Plant origin	Piperine
	Quercetin
	Curcumin
	Allicin

	Glycyrrhizin
	Naringin
	Steviosol
	Niaziridin
	Lysergol
	Emodin
	Simomenine
	Genistein
	5-methoxy hydnocarpin
	Capsaicin
	Capmul
	Camptothecin
	Gallic acid
	Ellagic acid
	Ferulic acid
Animal origin	Cow urine
	Cow urine distillate
	Chitosan

Piperine

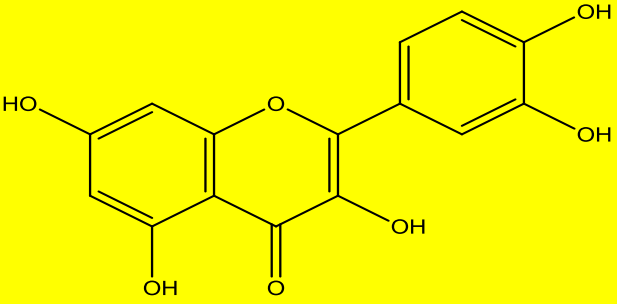
Piperine is an alkaloid obtained from the plant *Piper nigrum* and *Piper longum* belonging to the family piperaceae. The raw form of pepper is black coloured, normally used as spice and condiment. Its taste is pungent and it is not soluble in water. Other isomers of piperine like isopiperine, chavicine, isochavicine and piperanine are also available along with piperine in these plants. Piperine has been investigated for various pharmacological properties like neuroprotection, anti-inflammatory, antioxidant and anticancer properties, other than its drug penetration enhancement (1, 2). It has been reported to have bio enhancing effect on vaccines, pyrazinamide, indomethacin, phenytoin, ciprofloxacin ibuprofen and many more. (3)

(2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one
Chemical Formula: $C_{17}H_{19}NO_3$
Exact Mass: 285.14
Molecular Weight: 285.34
m/z: 285.14 (100.0%), 286.14 (18.7%), 287.14 (2.3%)
Elemental Analysis: C, 71.56; H, 6.71; N, 4.91; O, 16.82

Figure 1: Chemical structure of piperine

Quercetin

Quercetin is a natural polyphenolic compound categorized as a flavonoid, having antioxidant potential, It is abundantly available in variety of fruits (apple, grapes, berry and citrus fruits), grains, vegetables (broccoli, onions etc.), wine, coffee, green tea. It is also available in medicinal plants like *Hypericum perforatum*, *Ginkgo biloba* and *Sambucus canadensis*. Piperine has also been investigated for a range of medicinal properties like elevated drug permeability, anti-inflammatory, anti-allergic, antihypertensive, anti-cancer, cardio-protective, anti-viral and antioxidant potential owned via fighting with free radicals. It is also reported to be taken as supplement for energy boost-up (4, 5). It has been reported to enhance the bioavailability of verapamil, diltiazem, paclitaxel, digoxin, tamoxifen etc. (3)

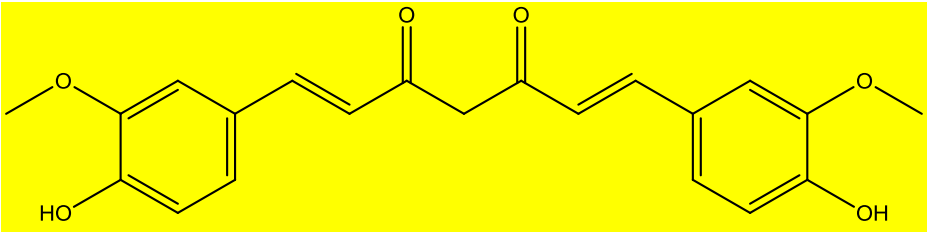


2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one
Chemical Formula: $C_{15}H_{10}O_7$
Exact Mass: 302.04
Molecular Weight: 302.24
m/z: 302.04 (100.0%), 303.05 (16.6%), 304.05 (2.7%)
Elemental Analysis: C, 59.61; H, 3.33; O, 37.06

Figure 2: Chemical structure of quercetin

Curcumin

Curcumin is a brilliant yellow to orangish yellow coloured compound obtained from *Curcuma longa* (turmeric) belonging to the family Zingiberaceae. Turmeric is known as the wonder drug in the Indian traditional medicine system, as it is used for the treatment of massive number of ailments. It is the major compound of the turmeric extract (Curcumin - 60–70%, demethoxycurcumin - 20–27%, bisdemethoxycurcumin - 10–15%) and widely used in herbal medicines, cosmetics, and food industry as a colouring and flavouring agent. Curcumin is a natural phenolic compound responsible for yellow colour of turmeric. It is used as antiviral, antibiotic and anticancer agent. (6, 7)

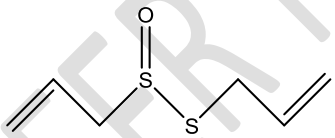


(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
Chemical Formula: $C_{21}H_{20}O_6$
Exact Mass: 368.13
Molecular Weight: 368.38
m/z: 368.13 (100.0%), 369.13 (23.2%), 370.13 (3.7%)
Elemental Analysis: C, 68.47; H, 5.47; O, 26.06

Figure 3: Chemical structure of curcumin

Allicin

Allicin is a sulphurous organic chemical compound obtained from the plant Alium sativum (garlic) belonging to the family alliaceae. It is light yellow coloured oily substance that is accountable for distinctive odour of garlic. Biologically it is used in the treatment of septicaemia occurring due to virus and fungus and as an antioxidant. (8, 9) It has been found to have bio-enhancing effect on Amphotericin-B and many other drugs. (3)

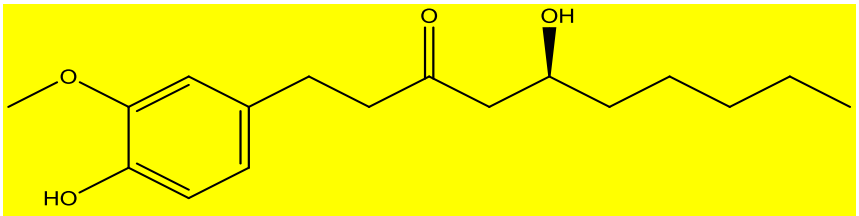


S-allyl prop-2-ene-1-sulfinothioate
Chemical Formula: $C_6H_{10}OS_2$
Exact Mass: 162.02
Molecular Weight: 162.27
m/z: 162.02 (100.0%), 164.01 (9.0%), 163.02 (6.5%), 163.02 (1.6%)
Elemental Analysis: C, 44.41; H, 6.21; O, 9.86; S, 39.52

Figure 4: Chemical structure of allicin

Ginger

It is the rhizome part of the plant *Zingiber officinale* belonging to family Zingiberaceae. The rhizomes of ginger are popularly used as flavouring agent in food, whereas the dried ginger is used a spice and condiment. The colour of the rhizome varies depending on the variety from yellowish white to light brown with some purplish patches. Traditionally, ginger is provided with lots of health benefits like preventing motion sickness, headache, nausea, and vomiting. It also shows anti-inflammatory potential due to presence of gingerol, anti-cancer mainly towards colorectal cancer and it also helps in killing tumour cells in case of ovarian cancer. It is reported to be acting as an immuno-booster in various research studies and ancient literature (10,11,12,13,14). It is found to be possessing bioenhancing effect on Azithromycin, Erythromycin, Cephalexin, Cefadroxil, Amoxycillin, Cloxacillin etc. (3)

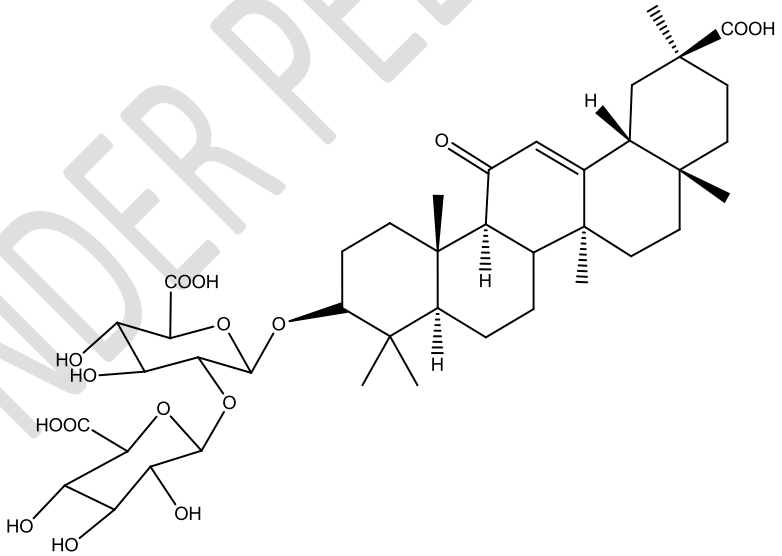


(*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one
Chemical Formula: $C_{17}H_{26}O_4$
Exact Mass: 294.18
Molecular Weight: 294.39
m/z: 294.18 (100.0%), 295.19 (18.8%), 296.19 (2.5%)
Elemental Analysis: C, 69.36; H, 8.90; O, 21.74

Figure 5: Chemical structure of gingerol

Glycyrrhizin

Glycyrrhizin is the sweetening constituent derived from the root of plant *Glycyrrhiza glabra* (mulethi). It is extensively used as the sweetening agent in various pharmaceutical and nutraceutical preparations. Along with it, the use of this herb is also reported to be as flavouring agent in food and beverage industry, as conditioner as well as humectant in cosmetics for preserving moisture content. In the traditional system of medicine, it is reported to be very useful in the treatment of cough, sore throat, severe hepatitis condition at predefined amounts. An interesting fact about this drug is that at high doses it may lead to high blood pressure and electrolyte imbalance (15,16). It is reported to be a potential source of increasing bioavailability of rifampicin, tetracycline, nalidixic acid, ampicillin some other antibiotics. (3)

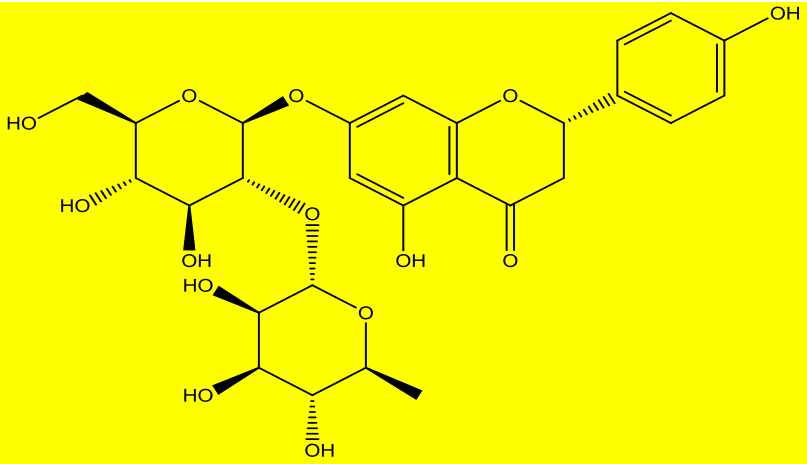


6-(((3*S*)-6-carboxy-2-(((3*R*,4a*R*,6b*S*,8a*S*,12a*R*,14a*S*,14b*S*)-11-carboxy-4,4,6b,8a,11,14b-hexamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yl)oxy)-4,5-dihydroxytetrahydro-2*H*-pyran-3-yl)oxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid
Chemical Formula: $C_{41}H_{60}O_{16}$
Exact Mass: 808.39
Molecular Weight: 808.91
m/z: 808.39 (100.0%), 809.39 (45.6%), 810.39 (12.9%), 811.40 (3.0%)
Elemental Analysis: C, 60.88; H, 7.48; O, 31.65

Figure 6: Chemical structure of glycirrhizin

Naringin

It is a naturally occurring flavonoid available in citrus fruits (bergamot, orange, lemon, mandarin), grapes and is responsible for the sour taste of these fruits. It possesses powerful anti-inflammatory, antioxidant property and is used in treatment of obesity, high blood sugar and high blood pressure. This is also used in food industry as flavouring agent and to improve the texture of the food. It is also used prevent bitterness in case of canned citrus food.In pharmaceutical industry it is explored for its bioenhancing potential (17, 18). It is reported to enhance the bioavailability of Verapamil, Tamoxifen, Quinine, Clopidogrel, nimodipine, diltiazem etc. (3)



(*S*)-7-(((2*S*,3*R*,4*S*,5*S*,6*R*)-4,5-dihydroxy-6-(hydroxymethyl)-3-(((2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)oxy)-5-hydroxy-2-(4-hydroxyphenyl)chroman-4-one
Chemical Formula: $C_{27}H_{32}O_{14}$
Exact Mass: 580.18
Molecular Weight: 580.53
m/z: 580.18 (100.0%), 581.18 (29.7%), 582.19 (4.4%), 582.18 (2.9%), 583.19 (1.3%)
Elemental Analysis: C, 55.86; H, 5.56; O, 38.58

Figure 7: Chemical structure of naringin

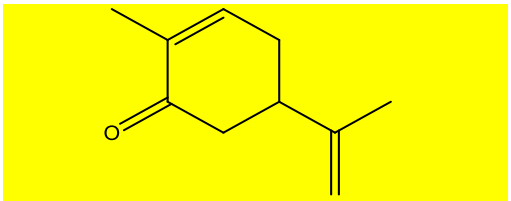
Cuminum

The seeds of the plant *cuminum cyminum* belonging to the family apiaceae are used extensively as carminative in the traditional system of medicine in India. These are dark brown coloured seeds with aromatic flavour (cuminaldehyde, cymene, terpinoids) and used as spice. It helps in the treatment of belching, gastric refreshment, removal of helminthes from gastrointestinal tract. Oil (essential oil) derived from the seeds of cuminum is used in cosmetics and is reported to be responsible for its bioenhancer potential (19, 20). It is reported to improve the bioavailability of Ketoconazole, Erythromycin, Fluorouracil, Amoxycillin, Fluconazole, Cephalexin, Zidovudine etc. (3)

Carum carvi

The seeds obtained from the plant of *Carum carvi* belonging to the family apiaceae is commonly known as caraway. It is having similarities with the seeds of plant *cuminum cyminum* in terms of their shape and size. The aroma of the seeds is due to carvone, limonene and anethole. Caraway seeds are used as carminative and it is reported to be very useful in providing an effective relief from burping, loosening the bowel for easy defecation,

and it also helps in elimination of excess body fluids via diuresis. They improved plasma concentration of antiviral, antifungal, antibiotics and chemotherapy drugs have been reported in the presence of caraway. (21, 22)

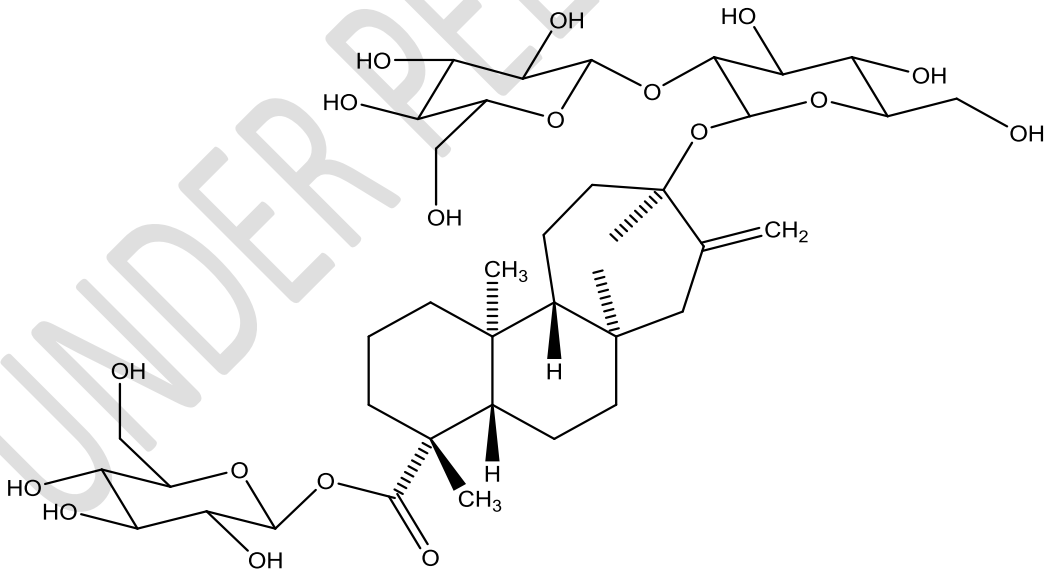


2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone
Chemical Formula: $C_{10}H_{14}O$
Exact Mass: 150.10
Molecular Weight: 150.22
m/z: 150.10 (100.0%), 151.11 (11.0%)
Elemental Analysis: C, 79.96; H, 9.39; O, 10.65

Figure 8: Chemical structure of carvone

Stevia

Stevia is known for its sweetening potential and is reported to be many times sweeter than sugar. It is obtained from the leaves of the plant *Stevia rebaudiana*. The sweetness is owed to the presence of two glycosides stevioside and rebaudioside. It is explored to be used as an additive, food supplement and an alternate to sugar as well as synthetic sweeteners, especially for the benefit of the diabetic patients and elderly people which help in low intake calories. (23, 24, 25, 27) It has also been explored for it bioenhancing activity in the last few decades, demonstrating it as its active potential.

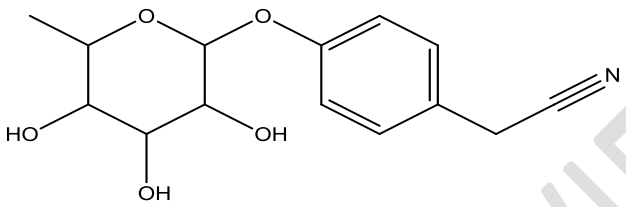


Chemical Formula: $C_{39}H_{64}O_{18}$
Exact Mass: 820.41
Molecular Weight: 820.92
m/z: 820.41 (100.0%), 821.41 (42.2%), 822.42 (8.7%), 822.41 (3.7%), 823.42 (1.6%)
Elemental Analysis: C, 57.06; H, 7.86; O, 35.08

Figure 9: Chemical structure of stevioside

Niaziridin

Niaziridin is a glycoside extracted from the leaves, pods and bark of the plant *Moringa oleifera*. Medicinally it is well known to be used in the treatment of arthritic pain, and hyperlipidaemia, along with its anti-teratogenic potential to provide protection to the embryo and foetus. As per the Indian traditional system of medicine it is also used for its potential activities such as hepatoprotection, anti-fertility, anti-microbial, anti-fungal, anti-cancer, anti-inflammatory, spasmolytic, anti-ulcer and antioxidant profile. (28, 29) It is found to have bio-enhancing effect on anti-fungal drugs etc. (3)

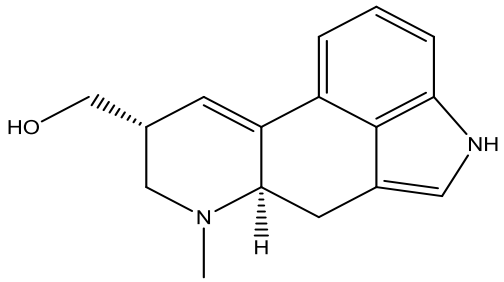


2-(4-((3,4,5-trihydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)phenyl)acetonitrile
Chemical Formula: $C_{14}H_{17}NO_5$
Exact Mass: 279.11
Molecular Weight: 279.29
m/z: 279.11 (100.0%), 280.11 (15.7%), 281.12 (1.1%), 281.11 (1.1%)
Elemental Analysis: C, 60.21; H, 6.14; N, 5.02; O, 28.64

Figure 10: Chemical structure of niaziridin

Lysergol

It is a clavinet alkaloid belonging to the class of ergoline and is obtained from the plant *Rivea corymbosa* belonging to family convolvulaceae. It is also reported to be present in very small amount in the claviceps group of fungi, and the seeds of the plant *Ipomoea muricata*. Medicinally it is reported to have neuroleptic properties and thus is used for treating psychosis, especially post-surgical psychosis. It is also reported to be used as a psychotropic analgesic, hypotensive and uterus as well as intestine stimulant. But is found to have many neurological side effects like, hallucinations, seizures, delirium, burning sensations and gangrene. (30, 31) The limitations of its side effect and its potential to enhance the bioavailability of the drugs has given a new direction to explore this active alkaloid.

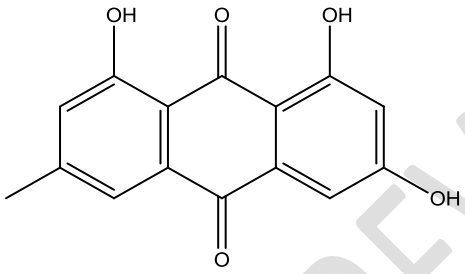


((6a*R*,9*R*)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanol
Chemical Formula: $C_{16}H_{18}N_2O$
Exact Mass: 254.14
Molecular Weight: 254.33
m/z: 254.14 (100.0%), 255.15 (17.6%), 256.15 (1.7%)
Elemental Analysis: C, 75.56; H, 7.13; N, 11.01; O, 6.29

Figure 11: Chemical structure of lysergol

Aloe vera

Aloe vera is a plant with succulent and thick leaves belonging to the family asphodelaceae and reported to be used traditionally for the treatment of number of ailments. The leaves of this plant contains gel and mainly comprising of constituents like anthraquinones (emodin, lectin), mannans, polymannans and, anthrones. The gel separated from the leaves is used in the preparation of topical products for skin care, burns and cosmetic preparations (32, 33, 34, 35, 36). The juice of this plant is also reported to be used for weight loss and digestant property along with its use as a food in desert areas of India. It is also used for its emollient and skin hydration property and is thus applied directly on the skin surface for its protective action. It is also used as a thickening and protective agent in variety of cosmetic products. It has also been envisaged for its potential to increase the absorption of vitamins and insulin. (3)

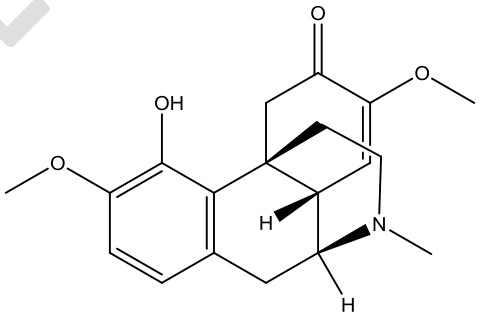


1,3,8-trihydroxy-6-methylanthracene-9,10-dione
Chemical Formula: $C_{15}H_{10}O_5$
Exact Mass: 270.05
Molecular Weight: 270.24
m/z: 270.05 (100.0%), 271.06 (16.5%), 272.06 (2.3%)
Elemental Analysis: C, 66.67; H, 3.73; O, 29.60

Figure 12: Chemical structure of emodin

Sinomenine

An alkaloid obtained from the roots of climber *Sinomenium acutum* and also known by the name of cocculine. It is used as an herbal medicine for the treatment of joint pain and inflammation (37). It is reported to be having bioenhancing effect on digoxin, quinidine, paeniflorin, verapamil etc. (3)

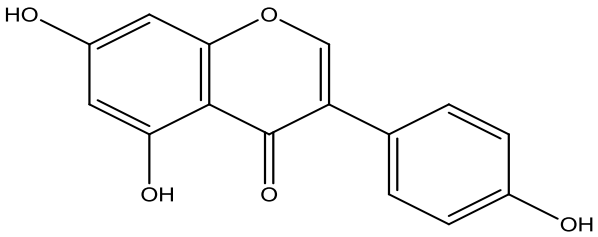


(4b*R*,8a*S*,9*S*)-4-hydroxy-3,7-dimethoxy-11-methyl-9,10-dihydro-5*H*-9,4b-(epiminoethano)phenanthren-6(8a*H*)-one
Chemical Formula: $C_{19}H_{23}NO_4$
Exact Mass: 329.16
Molecular Weight: 329.39
m/z: 329.16 (100.0%), 330.17 (21.0%), 331.17 (2.9%)
Elemental Analysis: C, 69.28; H, 7.04; N, 4.25; O, 19.43

Figure 13: Chemical structure of sinomenine

Genistein

Isoflavone derived from the plant *Genista tinctoria, Glycine max and Pueraria lobata*; also called as growth inhibitor and phytoestrogen. Biologically found to have antioxidant, anthelmintic, anti-cancer and atherosclerosis potential (38, 39, 40, 41). In various research studies it has been proven that genistein can enhance the bioavailability of two anticancer drugs namely paclitaxel and vinblastine. (3)

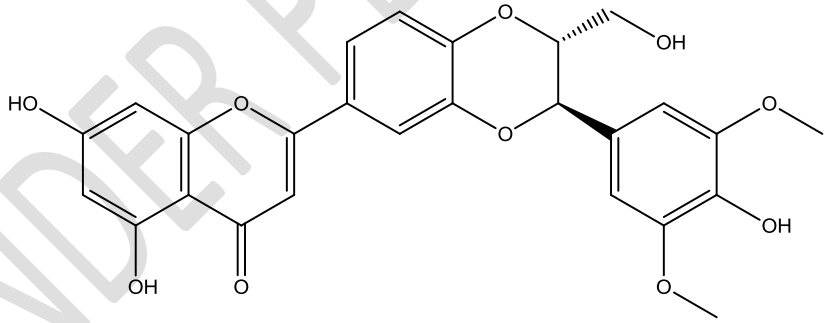


5,7-dihydroxy-3-(4-hydroxyphenyl)-4*H*-chromen-4-one
Chemical Formula: $C_{15}H_{10}O_5$
Exact Mass: 270.05
Molecular Weight: 270.24
m/z: 270.05 (100.0%), 271.06 (16.5%), 272.06 (2.3%)
Elemental Analysis: C, 66.67; H, 3.73; O, 29.60

Figure 14: Chemical structure of genistein

5-Methoxyhydnocarpin (5-MHC)

5-MHC is obtained from the plant *Hydnocarpus wightianus*, as well as berberis species; chemically it is an amphipathic weak acid. It is one of the active components of chaulmoogra oil, used for the treatment of leprosy traditionally. It is found to have anti-cancer activity and enhances the antimicrobial activity of berberine. (42, 43, 44)

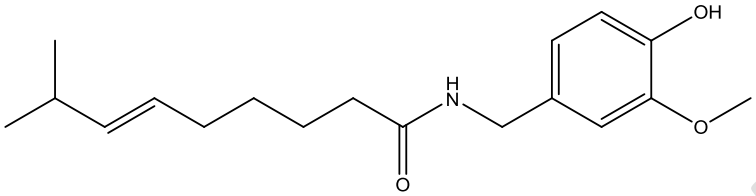


5,7-dihydroxy-2-((2*R*,3*R*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-4*H*-chromen-4-one
Chemical Formula: $C_{26}H_{22}O_{10}$
Exact Mass: 494.12
Molecular Weight: 494.45
m/z: 494.12 (100.0%), 495.12 (28.1%), 496.13 (6.0%)
Elemental Analysis: C, 63.16; H, 4.48; O, 32.36

Figure 15: Chemical structure of 5-Methoxyhydnocarpin

Ammannia multiflora

Herbaceous plant often called as many flower ammannia belonging to family Lythraceae. Used commercially as decorative purpose and in the preparation of baked food. It has been reported that it contains ammaniol, an alcoholic compound to have bio-enhancing potential. Found to have bio-enhancing effect on anti-microbial agents and few antibiotics like nalidixic acid. (45, 46)

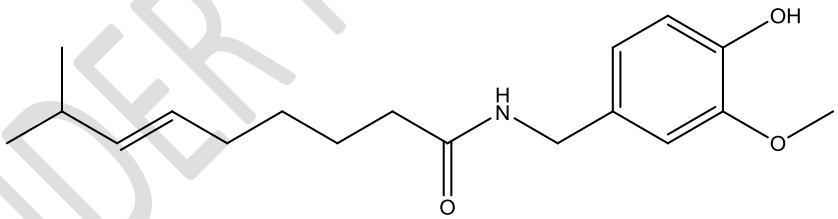


(*E*)-*N*-(4-hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide
Chemical Formula: $C_{18}H_{27}NO_3$
Exact Mass: 305.20
Molecular Weight: 305.41
m/z: 305.20 (100.0%), 306.20 (20.0%), 307.21 (1.9%)
Elemental Analysis: C, 70.79; H, 8.91; N, 4.59; O, 15.72

Figure 16: Chemical structure of ammaniol

Capsaicin

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is one of the active phytoconstituents found in the plants of genus capsicum i.e., Chilli peppers. Capsaicin and its chemical constituents together are called as capsaicinoids; found to be causing irritation and burning sensation when encounters the skin surface. It is reported to be used in the formulations used topically for pain relief caused by aches, arthritis, back pain, etc. Also found to reduce peripheral neuropathy, post-herpetic neuralgia, diabetic neuropathy, and cardiovascular diseases. It has been reported to be showing bio-enhancing effect on theophylline and fexofenadine. (47, 48, 49, 50)



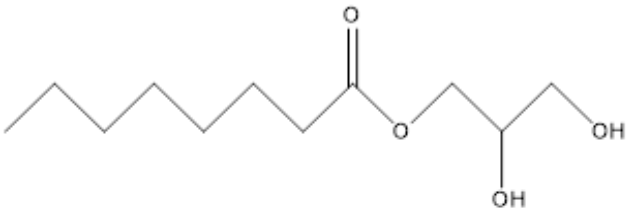
(*E*)-*N*-(4-hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide
Chemical Formula: $C_{18}H_{27}NO_3$
Exact Mass: 305.20
Molecular Weight: 305.41
m/z: 305.20 (100.0%), 306.20 (20.0%), 307.21 (1.9%)
Elemental Analysis: C, 70.79; H, 8.91; N, 4.59; O, 15.72

Figure 17: Chemical structure of capsaicin

Capmul

Capmul is a diversified group of multifunctional lipids, majorly mono and diglycerides, obtained from vegetable oil fatty acids and esterification of propylene glycol and glycerine with certain vegetable oil fatty acids. It is

used as an emulsifying agent and widely used to enhance bioavailability, solubility, and penetration. (51) One of the major components of capmul is monocaprylin.

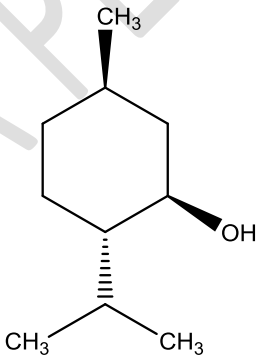


Chemical Formula: $C_{11}H_{22}O_4$
Exact Mass: 218.15
Molecular Weight: 218.29
m/z: 218.15 (100.0%), 219.16 (11.9%)
Elemental Analysis: C, 60.52; H, 10.16; O, 29.32

Figure 18: Chemical structure of monocaprylin

Peppermint oil

Peppermint oil is the volatile oil extracted from the plant belonging to the mint family, especially *Mentha piperita*. The two important chemical constituents of peppermint oil are menthone, and menthol which are used as insect repellents and are used traditionally for treatment of variety of ailments. Medicinally menthol is used in the treatment of irritable bowel syndrome, neuropathy, muscle pain, itching, decongestion, and to reduce heart burns. (52, 53, 54, 55, 56, 57) Menthol is a cyclic alcohol and more specially is classified as monoterpenoid, which can also be synthesized synthetically in the laboratory.

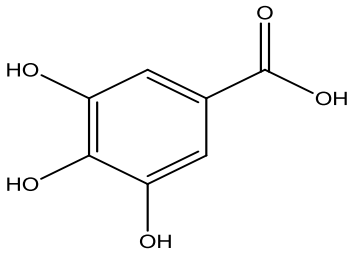


Chemical Formula: $C_{10}H_{20}O$
Exact Mass: 156.15
Molecular Weight: 156.27
m/z: 156.15 (100.0%), 157.15 (10.8%)
Elemental Analysis: C, 76.86; H, 12.90; O, 10.24

Figure 19: Chemical structure of menthol

Gallic acid

Gallic acid is a solid phenolic acid commonly found in variety of plants like sumac, witch, tea leaves, hazel, gallnuts, oak bark etc. It is synthesized by the process of hydrolysis of tannins and the products are called gallotannins and ellagitannins. It is reported to be used as antioxidant, anti-hyperlipidaemic and commercially as writing ink, along with its utilization in the process of tanning process and manufacturing of paper. It has also shown bio-enhancing effect on anti-viral drugs, diltiazem, metoprolol etc. (58, 59, 60)

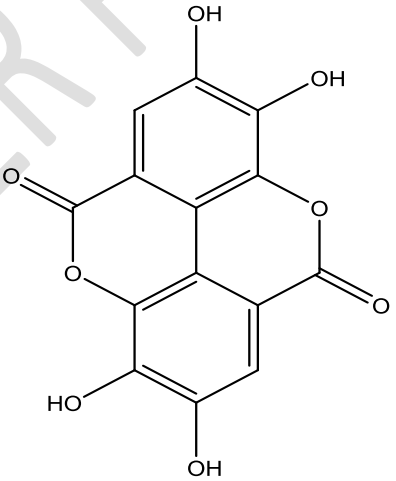


3,4,5-trihydroxybenzoic acid
Chemical Formula: $C_7H_6O_5$
Exact Mass: 170.02
Molecular Weight: 170.12
m/z: 170.02 (100.0%), 171.02 (7.6%), 172.03 (1.3%)
Elemental Analysis: C, 49.42; H, 3.55; O, 47.02

Figure 20: Chemical structure of gallic acid

Ellagic acid

Ellagic acid is a phenolic compound found in vegetables and fruits like walnuts, pecans, cranberries, raspberries, strawberries, chestnuts, grapes, peaches and pomegranates. Used as antioxidant and anti-proliferative agent. Medicinally used as dietary additive, anti-cancer agent and in curing heart diseases. (61, 62, 63, 64, 65, 66)

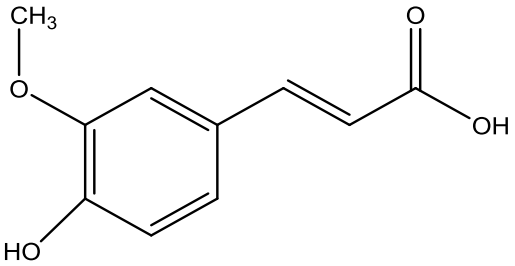


Chemical Formula: $C_{14}H_6O_8$
Exact Mass: 302.01
Molecular Weight: 302.19
m/z: 302.01 (100.0%), 303.01 (15.1%), 304.01 (1.6%), 304.01 (1.1%)
Elemental Analysis: C, 55.64; H, 2.00; O, 42.35

Figure 21: Chemical structure of gallic acid

Ferulic acid

Ferulic acid is an organic phenol compound found in plant cell walls mainly fennel ferula communis. It is found in vegetables mainly bamboo shoot, popcorn, flaxseed and barley grain, bran, wheat. It is used in the treatment of osteoporosis, Alzheimer's disease, atherosclerosis, cancer, hyperlipidaemic condition, diabetes, menopause problems, and antioxidant and in skin treatment. (67, 68, 69, 70, 71, 72)

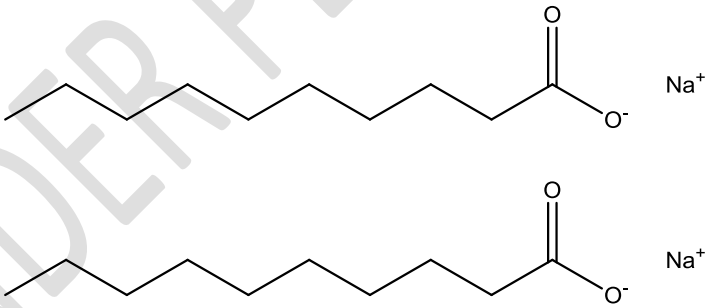


Chemical Formula: $C_{10}H_{10}O_4$
Exact Mass: 194.06
Molecular Weight: 194.19
m/z: 194.06 (100.0%), 195.06 (10.8%)
Elemental Analysis: C, 61.85; H, 5.19; O, 32.96

Figure 22: Chemical structure of ferulic acid

Sodium Caprate

Sodium caprate is a natural compound known to be used as one of the efficient intestinal permeation enhancers, majorly used in the delivery of macromolecules. It is the sodium salt of an aliphatic saturated 10-carbon medium chain fatty acid i.e., capric acid. It is also enlisted as the FDA approved food additive. (73, 74)



sodium decanoate
Chemical Formula: $C_{20}H_{38}Na_2O_4$
Exact Mass: 388.26
Molecular Weight: 388.49
m/z: 388.26 (100.0%), 389.26 (22.2%), 390.26 (3.1%)
Elemental Analysis: C, 61.83; H, 9.86; Na, 11.84; O, 16.47

Figure 23: Chemical structure of sodium caprate

Mechanism of action of Bioenhancers:

There are variety of mechanisms reported in several research studies regarding the permeation enhancing potential of different bioenhancers. Few of these mechanisms are illustrated here under in the figure:

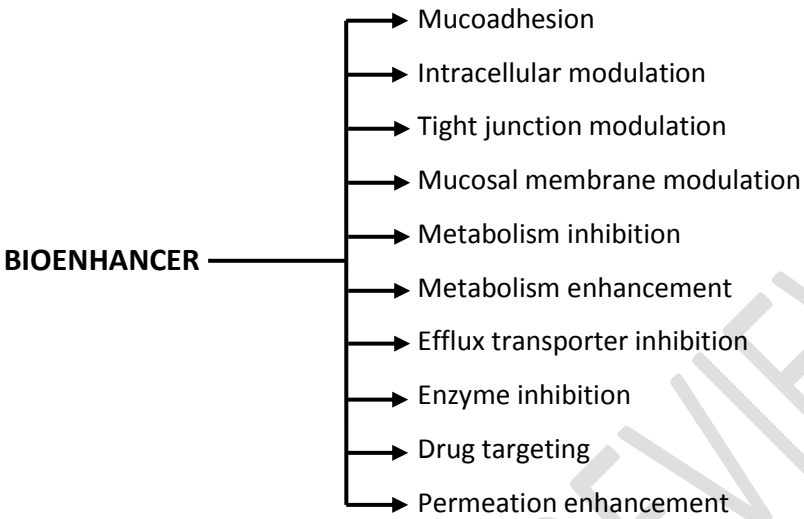


Figure 24: Mechanism of action of bioenhancers

Conclusion

It is evident from number of research studies that most of the newly developed pharmaceutically active compounds, especially the biomacromolecules like proteins and peptides have either lower bioavailability or lower biostability. In this direction the bioenhancers are the right choice of compounds to overcome these limitations. Even though the surfactants can be an effective solution but naturally occurring bioenhancers are preferred over these because of safety, biocompatibility, low cost and abundant availability. This results in reduction of cost, toxic side effects, and lower drug dose which in turn assure better therapeutic profile. Therefore, this article emphasized on the significance of naturally occurring bioenhancers and their aiming to highlight the need of exhaustive exploration of natural resources as well processing of established naturally occurring bioenhancers to design innovative and efficient drug delivery system. So further research studies must be continued in developing new formulations using these bio-enhancers to target efficient and affordable drug delivery system availability to the economically weaker sections of the society.

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