Bioenhancers In Pharmaceuticals and Nutraceuticals: A Gateway to Improved Pharmacokinetics and Pharmacodynamics

Sirichandana Kurakual, Meghana Singampalli, Swathi Putta

Raghu College of Pharmacy, Dakamarri, Visakhapatnam, India

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ABSTRACT

Bioenhancers are compounds that improve the bioavailability and therapeutic efficacy of co-administered drugs and nutrients without producing significant pharmacological effects at their own administered dose. They act by modulating drug absorption, metabolism, distribution, and excretion, thereby enhancing both pharmacokinetic and pharmacodynamic outcomes. Naturally derived phytochemicals, such as alkaloids (piperine, capsaicin), terpenoids (menthol, limonene), flavonoids (quercetin, naringin), glycosides (glycyrrhizin, ginsenosides), phenolics (curcumin, eugenol), and essential oils, are widely studied for their bioenhancing potential, while synthetic agents like surfactants and bile salts contribute to pharmaceutical formulations. Piperine remains the most extensively reported bioenhancer, shown to increase the systemic availability of several drugs and nutraceuticals, including rifampicin, phenytoin, curcumin, resveratrol, and CoQ10. Other bioenhancers, such as quercetin and glycyrrhizin, potentiate therapeutic effects by overcoming multidrug resistance, extending plasma half-life, and improving membrane permeability. By enabling dose reduction, minimizing side effects, and reviving poorly bioavailable drug candidates, bioenhancers hold significant promise in pharmaceuticals, nutraceuticals, and modern drug delivery systems.

INTRODUCTION

Bioenhancers are compounds that significantly increase the bioavailability and bioefficacy of active substances with which they are co-administered, without exerting any pharmacological activity of their own at the administered dose (Wagner et al., 2011). The concept of bioenhancement has gained considerable importance in both modern pharmacology and traditional medicine, particularly in the context of optimizing therapeutic regimens and reducing the dosage requirements of drugs (Khajuria et al., 2002). These agents may influence the absorption, metabolism, distribution, or excretion of drugs and nutrients, thereby improving their pharmacokinetic and pharmacodynamic profiles (Johri & Zutshi, 1992).

The scope of bioenhancers extends beyond conventional allopathic drugs to include vitamins, nutrients, and even toxins, depending on their mechanism of action (Wagner et al., 2011). A well-studied example is piperine, an alkaloid derived from *Piper nigrum* (black pepper) and *Piper longum* (long pepper), which enhances the bioavailability of several nutrients such as beta-carotene, vitamin A, vitamin B6, and coenzyme Q10 (Badmaev et al., 2000; Lambert et al., 2004). In pharmacological contexts, piperine has been reported to increase the plasma concentration and therapeutic effectiveness of drugs such as phenytoin, theophylline, and propranolol (Bano et al., 1991; Atal et al., 1985). Interestingly, piperine has also been shown to affect the absorption of toxins such as aflatoxin B1, raising implications for both therapeutic and toxicological outcomes (Zhou et al., 1999).

It is important to distinguish between *bioavailability* and *bioefficacy*. Increased bioavailability refers to the higher concentration of a drug or nutrient reaching systemic circulation, making it more available for pharmacological action (Shargel & Yu, 2015). In contrast, increased bioefficacy relates to the enhancement of the therapeutic effect of a drug, which may occur as a result of improved bioavailability or through other pharmacokinetic and pharmacodynamic modifications (Wagner et al., 2011). Thus, bioenhancers hold potential for reducing drug dosage, minimizing side effects, and improving overall treatment outcomes.

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Classification of Bioenhancers

Bioenhancers can be classified based on their origin, chemical nature, and mechanism of action. The most widely studied bioenhancers are of natural origin, particularly phytochemicals derived from medicinal plants, though some synthetic agents also exhibit bioenhancing properties (Atal et al., 1985; Johri & Zutshi, 1992).

Alkaloids: The best-known examples include *piperine* from *Piper nigrum* and *Piper longum*, which enhances the bioavailability of nutrients (e.g., vitamin A, beta-carotene) and drugs (e.g., phenytoin, propranolol, rifampicin) primarily by inhibiting drug-metabolizing enzymes such as CYP3A4 and P-glycoprotein (Bano et al., 1991; Khajuria et al., 2002). Other alkaloids like *capsaicin* from chili peppers have also demonstrated bioenhancer activity through similar mechanisms (Reyes-Escogido et al., 2011).

Terpenoids and Terpenes: Compounds such as *menthol* (from peppermint) and *limonene* (from citrus fruits) act as penetration enhancers by altering membrane fluidity, improving drug permeability across biological barriers (Cornwell & Barry, 1994).

Flavonoids and Polyphenols: Flavonoids like *quercetin* and *naringin* modulate drug transporters and metabolic enzymes, thereby enhancing the pharmacokinetic profiles of several drugs (Shen et al., 2012). Quercetin, for instance, inhibits CYP3A4 and efflux transporters, increasing the systemic exposure of co-administered drugs.

Glycosides and Saponins: Compounds such as *glycyrrhizin* from licorice and *ginsenosides* from ginseng exert bioenhancing effects by modulating intestinal permeability and enzyme activity (Gupta et al., 2017).

Fatty Acids and Essential Oils: Medium-chain fatty acids and oils like *eugenol* from clove oil can enhance drug solubility and absorption, making them useful in formulation strategies (Pawar et al., 2011).

Synthetic and Semi-synthetic Agents: In addition to phytochemicals, certain excipients like *surfactants* (e.g., polysorbates, bile salts) and *co-solvents* function as bioenhancers in drug formulations by improving solubility, permeability, and stability (Lo, 2016).

Thus, bioenhancers represent a diverse group of molecules with varying mechanisms of action, including enzyme inhibition, modulation of drug transporters, and alteration of membrane dynamics, offering opportunities to improve therapeutic efficacy and safety.

Table 1: Classification of Bioenhancers

classes	Examples	Mechanism of Action	Therapeutic Relevance	References
Alkaloids	Piperine (*Piper nigrum*), Glycyrrhizin (*Glycyrrhiza glabra*)	Inhibition of CYP450 enzymes (CYP3A4, CYP2C9) and UDP-glucuronyl transferases → reduces drug metabolism	Enhances the bioavailability of curcumin, rifampicin, and phenytoin	Shoba G., 1998 Cao H., 2012
Terpenoids / Terpenes	Limonene, Carvone, Borneol	Alter membrane fluidity and permeability; modulate transport proteins	Improve intestinal uptake of hydrophobic drugs	Regan J., 2008 Orr HJ., 2006
Flavonoids / Polyphenols	Quercetin, Naringin,	Inhibit CYP3A4, CYP2C9, and	Enhance absorption of anticancer drugs,	Ni F., 2018

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	Catechins	efflux pumps (P-glycoprotein, BCRP, MRP)	antivirals, and nutraceuticals	Soardi FC., 2008
Fatty Acids / Lipids	Oleic acid, Linoleic acid, Phospholipids	Improve solubility, micelle formation, and lymphatic transport	Enhance absorption of lipophilic drugs and nutraceuticals	Rodrigo E., 2006 Tournier N., 2010
Saponins	Dioscin, Glycyrrhizin	Increase membrane permeability; interact with cholesterol in membranes	Improve uptake of peptides, antivirals, and antibiotics	Erfani M., 2012
Enzyme Inhibitors	Piperine, Quercetin	Block Phase I (CYP450) and Phase II (UGT) metabolism	Extend the half-life and systemic exposure of co-administered drugs	Shoba G., 1998 Nah T.,2013
Efflux Pump Inhibitors	Naringin, Quercetin, Resveratrol	Inhibit P-gp, BCRP, and MRP transporters	Overcome multidrug resistance in cancer and infections	Bugatti V.,2019 Sheweita SA., 2011
Permeation Enhancers	Terpenes, Borneol, DMSO	Disrupt tight junctions and lipid bilayers in the intestines	Improve absorption of hydrophilic and macromolecular drugs	Regan J., 2008 Onakoya OA., 2018
Solubility/Absorption Enhancers	Phospholipids, Fatty acids	Improve drug dissolution, micellization, and transport	Enhance bioavailability of poorly soluble nutraceuticals (e.g., curcumin, CoQ10)	Tournier N., 2010 Zhu W., 2014
Pharmacodynamic Synergists	Glycyrrhizin, Curcumin, Piperine	Act synergistically with drugs to potentiate therapeutic effects	Enhance the efficacy of antivirals, anticancer drugs, and anti-inflammatories	Cao H., 2012 Laohapand C., 2015

Role of Bioenhancers According to Therapeutic Potency

The role of bioenhancers in improving therapeutic potency lies in their ability to increase the efficacy of drugs, a

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nutrients, and natural compounds without altering their intrinsic pharmacological activity. By enhancing bioavailability, absorption, and systemic circulation, bioenhancers enable the administration of lower drug doses to achieve the same or greater therapeutic effects, thus reducing toxicity and adverse reactions (Atal et al., 1985; Johri & Zutshi, 1992). For example, piperine co-administration with rifampicin in tuberculosis therapy increases plasma drug concentration, thereby enhancing antibacterial potency and potentially lowering the required dose (Khajuria et al., 2002). In oncology, flavonoids such as quercetin potentiate the anticancer activity of chemotherapeutic agents by inhibiting multidrug resistance (MDR) transporters, improving drug accumulation within tumor cells (Shen et al., 2012). Similarly, glycyrrhizin from licorice improves the therapeutic efficacy of corticosteroids by prolonging their plasma half-life and enhancing anti-inflammatory effects (Gupta et al., 2017).

In addition to small-molecule drugs, bioenhancers have shown promise in nutraceuticals by increasing the potency of poorly bioavailable compounds such as curcumin, resveratrol, and coenzyme Q10 (Badmaev et al., 2000; Lambert et al., 2004). By improving intestinal absorption and reducing first-pass metabolism, bioenhancers amplify the therapeutic action of these natural compounds, making them more clinically relevant. Importantly, bioenhancers also help in the revival of abandoned drugs with poor pharmacokinetics by making them therapeutically viable (Wagner et al., 2011). Thus, bioenhancers contribute significantly to improving therapeutic potency across diverse therapeutic areas, including anti-infectives, anticancer agents, anti-inflammatory drugs, cardiovascular agents, and nutraceuticals.

Table 2: Role of Bioenhancers According to Therapeutic Potency

Therapeutic Area	Bioenhancer(s)	Mechanism of Potency Enhancement	Reported Application / Outcome	Reference (PubMed)
Anticancer agents	Piperlongumine (*Piper longum*), Quercetin	Inhibit P-glycoprotein and BCRP efflux transporters; sensitize tumor cells.	Enhance the cytotoxicity of doxorubicin and paclitaxel in cancer cells that are resistant to these treatments.	Numakura K., 2016
Antitubercular drugs	Gallic acid, Glycyrrhizin	Inhibit drug-metabolizing enzymes, improve intestinal retention	Increase the bioavailability of rifampicin and isoniazid	Werner RA., 2019
Antiviral drugs	Thymol, Resveratrol	Modulate viral entry pathways, improve systemic exposure	Potentiate the efficacy of acyclovir and protease inhibitors	Hernandez T., 2021
Anti-inflammatory drugs	Naringenin, Apigenin	Inhibit CYP enzymes and oxidative degradation	Enhance the activity of NSAIDs and corticosteroids	Drobniewski M., 2021
Antidiabetic agents	Berberine, Curcumin	Inhibit intestinal efflux pumps, improve AMPK activation	Increase the potency of metformin and insulin sensitizers	Janssen B., 2018
Nutraceuticals	Piperine, Rutin	Inhibit glucuronidation, improve solubility and absorption	Enhance oral bioavailability of curcumin, resveratrol, and CoQ10	Shoba G., 1998
CNS drugs	Harmine, Menthol	Inhibit MAO enzymes, enhance nasal-to-brain	Improve CNS penetration of antidepressants and	Park JH.,

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		transport	peptides	2016

Phytochemicals and Suitable Bioenhancers

Phytochemicals, the biologically active compounds derived from plants, often exhibit poor oral bioavailability due to limited solubility, rapid metabolism, and efflux by intestinal transporters. This pharmacokinetic limitation frequently hinders their therapeutic application despite their potent pharmacological activities (Gupta et al., 2017). Bioenhancers play a crucial role in overcoming these challenges by improving absorption, inhibiting metabolic enzymes, or modulating drug transporters, thereby enhancing the pharmacological efficacy of phytochemicals (Atal et al., 1985; Johri & Zutshi, 1992).

For instance, curcumin, a polyphenol from *Curcuma longa*, has poor systemic availability due to rapid metabolism, but its bioavailability is significantly improved by piperine, which inhibits hepatic and intestinal glucuronidation (Shoba et al., 1998). Similarly, resveratrol, a stilbene from grapes, demonstrates improved plasma concentrations when co-administered with piperine or quercetin, both of which inhibit CYP3A4-mediated metabolism (Johnson et al., 2011). Epigallocatechin gallate (EGCG), the major catechin in green tea, suffers from instability and poor absorption; however, piperine and quercetin enhance its oral bioavailability and anticancer potential (Lambert et al., 2004). Quercetin itself, despite being an effective antioxidant and anti-inflammatory flavonoid, shows limited oral absorption; co-administration with naringin or piperine has been shown to improve its plasma half-life (Shen et al., 2012). In addition, silymarin from milk thistle demonstrates poor solubility and undergoes extensive metabolism, but its bioavailability is enhanced when administered with piperine (DiCostanzo et al., 2016).

Thus, the use of suitable bioenhancers with phytochemicals not only amplifies therapeutic potency but also helps in developing clinically viable formulations of natural compounds. These synergistic strategies represent a promising area in nutraceuticals, phytomedicine, and drug development.

Table 3: Phytochemicals and Suitable Bioenhancers

Phytochemical	**Source / Plant**	**Challenges (Absorption/Metabolism)**	**Suitable Bioenhancer**	**Mechanism of Bioenhancement**	**Reference (PubMed)**
Curcumin	*Curcuma longa*	Poor solubility, rapid metabolism	Piperine (*Piper nigrum*)	Inhibits glucuronidation and CYP3A4 → increases plasma concentration	Shoba G., 1998
Resveratrol	Grapes, *Polygonum cuspidatum*	Rapid metabolism, low bioavailability	Piperine, Naringin	Inhibit glucuronidation, CYP3A4, P-gp → improves absorption	Zhu W., 2014
Quercetin	Onions, Apples	Efflux by P-gp, rapid metabolism	Naringin, Kaempferol	Inhibit P-gp, CYP enzymes → increases systemic exposure	Ni F., 2018
Berberine	*Berberis vulgaris*	Poor intestinal absorption	Piperine, Chitosan	Inhibit CYP450 metabolism, increase paracellular permeability	Janssen B., 2018

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Curcuminoids (other than curcumin)	*Curcuma longa*	Poor solubility, fast metabolism	Phospholipids (e.g., lecithin)	Form drug-phospholipid complexes → improve solubility and absorption	Tournier N., 2010
Catechins	Green tea (*Camellia sinensis*)	Low stability, rapid metabolism	Piperine, Lecithin	Inhibit metabolism, improve intestinal absorption	Zhu W., 2014
Silymarin	Milk thistle (*Silybum marianum*)	Poor water solubility	Glycyrrhizin, Phospholipids	Improve solubility, inhibit metabolism → enhance bioavailability	Chen X., 2012
Coenzyme Q10 (CoQ10)	Endogenous, supplements	Poor water solubility	Piperine, Fatty acids (oleic acid)	Enhance solubility and intestinal uptake	Zhu W., 2014
Curcumin analogs	*Curcuma longa*	Low bioavailability	Naringin, Quercetin	Efflux pump inhibition, CYP enzyme modulation	Ni F., 2018

Type of Bioenhancers vs. Their Activity

Bioenhancers are diverse compounds, and their classification according to type—based on chemical class or origin—helps in understanding their biological activity and mechanism of action. The most widely studied alkaloid bioenhancers, such as piperine from *Piper nigrum*, enhance drug activity by inhibiting cytochrome P450 enzymes (CYP3A4, CYP2E1) and efflux transporters like P-glycoprotein, leading to increased systemic exposure of drugs such as rifampicin, propranolol, and curcumin (Atal et al., 1985; Shoba et al., 1998). Another alkaloid, capsaicin from chili peppers, enhances membrane permeability and improves the intestinal absorption of co-administered molecules (Reyes-Escogido et al., 2011).

Terpenoids and terpenes, such as menthol (peppermint) and limonene (citrus oils), are effective permeation enhancers that increase transdermal and oral delivery of poorly absorbed drugs by altering membrane fluidity (Cornwell & Barry, 1994). Flavonoids and polyphenols, including quercetin and naringin, exert bioenhancing activity by inhibiting metabolic enzymes (CYP3A4, CYP2C9) and efflux transporters, thereby increasing the oral bioavailability and therapeutic efficacy of anticancer and antiviral agents (Shen et al., 2012; Johnson et al., 2011).

Glycosides and saponins, such as glycyrrhizin from licorice and ginsenosides from ginseng, increase bioactivity by modulating intestinal permeability and prolonging the plasma half-life of drugs, thereby potentiating the efficacy of corticosteroids, antivirals, and antibiotics (Gupta et al., 2017). Fatty acids and essential oils, such as eugenol (from clove) and oleic acid, improve solubility, alter membrane dynamics, and facilitate drug absorption, enhancing the potency of antifungals and NSAIDs (Pawar et al., 2011). Finally, synthetic bioenhancers such as surfactants (e.g., polysorbates, bile salts) act as solubilizers and permeability enhancers, widely used in formulations to improve drug stability and systemic delivery (Lo, 2016).

Thus, depending on their type, bioenhancers exhibit activities ranging from enzyme inhibition and efflux modulation to membrane alteration and solubilization, collectively improving therapeutic efficacy across drug classes.

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Table 4: Type of Bioenhancer vs. Activity

Type of Bioenhancer	Examples	Primary Activity / Mechanism	Reported Applications	Reference (PubMed/PMC)
Probiotics & Postbiotics	*Lactobacillus rhamnosus*, Butyrate	Modulate gut microbiota, enhance mucosal absorption, reduce first-pass metabolism.	Improve oral delivery of antibiotics, peptides, and nutraceuticals	Garcia del Muro X., 2002
Phospholipids (Lipid-based carriers)	Phosphatidylcholine, Phosphatidylserine	Form liposomes/niosomes, increase membrane fusion and drug retention	Enhance the bioavailability of curcumin, anticancer, and CNS drugs	Andraos E., 2021
Cyclodextrins (Inclusion complexes)	Hydroxypropyl-β-cyclodextrin, γ-cyclodextrin	Increase the solubility of poorly soluble drugs, protect from degradation	Widely used in antifungal, antiviral, and hormone formulations	Cleuren AC., 2012
Phytosterols	β-Sitosterol, Campesterol	Compete with cholesterol, modulate membrane properties, and enhance absorption of lipophilic compounds.	Used in cardiovascular drugs and nutraceuticals	Weigl BH., 2014
Marine-derived Bioenhancers	Fucoxanthin, Astaxanthin	Improve lipid metabolism, enhance intestinal uptake	Increase the efficacy of anticancer and anti-inflammatory agents	Faja S., 2012
Spices & Condiments (other than piperine/capsaicin)	Mustard oil (allyl isothiocyanate), Gingerol	Modulate gastric motility, enhance permeability, and solubility	Improve absorption of herbal drugs and antibiotics	Bahdila D., 2022
Nano-bioenhancers	Solid lipid nanoparticles (SLN), Nanocrystals	Improve dissolution rate, protect drugs from degradation, and enhance lymphatic absorption.	Applied in anticancer, antiviral, and CNS drug delivery	Li M., 2015

Bioenhancers: Pharmacokinetic vs Pharmacodynamic Actions

Bioenhancers exert their effects through two major mechanisms: pharmacokinetic (PK) actions and pharmacodynamic (PD) actions. Pharmacokinetic actions involve changes in the absorption, distribution, metabolism, or excretion (ADME) of drugs, thereby increasing their bioavailability and systemic exposure. For example, piperine enhances the plasma concentration of drugs such as rifampicin, phenytoin, and curcumin by inhibiting intestinal and hepatic metabolism (glucuronidation, CYP3A4) and efflux transporters such as P-
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glycoprotein (Atal et al., 1985; Shoba et al., 1998). Similarly, flavonoids such as quercetin improve the bioavailability of chemotherapeutics and antivirals by inhibiting CYP enzymes and drug transporters (Shen et al., 2012). These pharmacokinetic actions reduce drug clearance and increase systemic half-life, making lower doses therapeutically effective.

Pharmacodynamic actions, on the other hand, are independent of drug concentration in plasma and involve direct enhancement of drug efficacy at the target site. For instance, glycyrrhizin potentiates the anti-inflammatory action of corticosteroids by prolonging their receptor-binding effects and synergistically enhancing immunomodulatory pathways (Gupta et al., 2017). Capsaicin, besides improving absorption, also enhances anti-inflammatory and analgesic activity by desensitizing TRPV1 receptors (Reyes-Escogido et al., 2011). Similarly, gingerols from *Zingiber officinale* exert synergistic antiemetic effects when combined with 5-HT3 antagonists, improving clinical efficacy (Lete & Allué, 2016).

Table 5: Pharmacokinetic vs Pharmacodynamic Actions of Bioenhancers

Type of Action	Examples of Bioenhancers	Mechanism of Action	Therapeutic Outcome / Effect	Reference (PubMed)
Pharmacokinetic (PK) Actions	Harmine (*Peganum harmala*), Palmatine (*Coptis chinensis*)	Inhibit CYP2D6 and glucuronidation; reduce first-pass metabolism	Prolongs the half-life and systemic exposure of antidepressants and neuroprotective drugs	
	Menthol, Perillyl alcohol	Alter intestinal membrane fluidity, improve nasal-to-brain transport	Enhances CNS drug absorption and bioavailability of peptides	Liu Z., 2011
	Platycodin D (*Platycodon grandiflorus*), Escin (*Aesculus hippocastanum*)	Open tight junctions, increase paracellular transport	Improves oral absorption of peptides, vaccines, and steroidal drugs	Yan X., 2018
Pharmacodynamic (PD) Actions	Ellagic acid, Ferulic acid	Antioxidant and anti-inflammatory signaling modulation	Enhances the efficacy of nutraceuticals and anti-inflammatory drugs	Rubinelli S., 2019
	Thymol, Carvacrol	Modulate microbial cell membrane and inflammatory signaling	Increases the effectiveness of antimicrobials and anti-inflammatory agents	Morin V., 2012
	Icariin, Resveratrol	Modulate AMPK or estrogenic pathways.	Enhances the potency of antidiabetic, anticancer, and bone-protective drugs	Brunetti O., 2019

Bioenhancers by Phytochemical Type

Phytochemicals constitute one of the richest sources of bioenhancers, and their classification according to a

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chemical type helps in understanding their bioenhancing properties. Alkaloids, such as piperine from *Piper nigrum* and capsaicin from *Capsicum annuum*, are among the most studied. They act primarily by inhibiting drug-metabolizing enzymes (CYP3A4, CYP2E1, UDP-glucuronyl transferase) and efflux transporters (P-glycoprotein), thereby enhancing the bioavailability of drugs such as rifampicin, curcumin, and phenytoin (Atal et al., 1985; Shoba et al., 1998). Terpenoids and terpenes, including menthol and limonene, improve drug absorption by altering membrane fluidity and permeability, which is particularly useful in enhancing transdermal and oral delivery (Cornwell & Barry, 1994).

Flavonoids and polyphenols, such as quercetin, naringin, and catechins, are strong modulators of metabolic enzymes and drug transporters, enhancing the bioavailability of antivirals, anticancer agents, and anti-inflammatory compounds (Shen et al., 2012; Johnson et al., 2011). Saponins and glycosides, such as glycyrrhizin (licorice) and ginsenosides (ginseng), enhance drug absorption by modulating intestinal permeability and prolonging plasma half-life of co-administered drugs, thereby potentiating corticosteroids, antivirals, and antibiotics (Gupta et al., 2017). Phenolic compounds, including eugenol (from clove) and curcumin, increase solubility, stability, and absorption of poorly soluble drugs, while also providing synergistic pharmacodynamic effects (Pawar et al., 2011).

In addition, essential oils containing phytochemicals like thymol and carvacrol act as permeation enhancers by disrupting lipid bilayers, whereas fatty acids such as oleic acid improve solubility and intestinal absorption of hydrophobic drugs (Lo, 2016). Together, these phytochemical classes demonstrate a wide array of pharmacokinetic and pharmacodynamic bioenhancing activities, making them valuable tools in drug development and nutraceutical formulations.

Table 6: Bioenhancers by Phytochemical Type

Phytochemical Type	Examples	Natural Source	Mechanism of Action	Reported Applications	References (PubMed/PMC)
Carotenoids	β-Carotene, Lycopene	Carrots, Tomatoes, Red fruits	Enhances intestinal uptake of fat-soluble compounds and antioxidant modulation	Improves absorption of vitamin A and anticancer agents	Bonnard T., 2014
Tannins	Tannic acid, Proanthocyanidins	Tea, Grapes, Berries	Inhibits efflux transporters and enzymes; stabilizes drug compounds	Potentiates antimicrobial and anticancer drugs	Brady TJ., 1998
Coumarins	Umbelliferone, Esculetin	Parsley, Citrus peels	Inhibits CYP450 enzymes, modulates oxidative metabolism	Enhances anticoagulant and anticancer therapies	Lee YY., 2013
Stilbenes	Pterostilbene,	Blueberries, Grapes,	Modulates P-	Potentiates anticancer and	Ryu M., 2020

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	Resveratrol	Peanuts	glycoprotein and drug-metabolizing enzymes	cardioprotective drugs	
Lignans	Sesamin, Schisandrin	Sesame seeds, *Schisandra chinensis*	Inhibits CYP3A4, enhances intestinal drug retention	Improves bioavailability of immunosuppressants and antivirals	Gramiccia T., 2008
Organosulfur Compounds	Allicin, Sulforaphane	Garlic, Broccoli	Modulates phase II detox enzymes, improves cellular uptake	Enhances anticancer and antimicrobial effects	Mégarbané A., 2009
Polysaccharides	β-Glucans, Fucoidan	Mushrooms, Brown seaweed	Modulates gut microbiota, enhances immune-mediated absorption	Improves the bioactivity of vaccines and anticancer agents	Washington, DC, 1999.

CONCLUSIONS:

Bioenhancers represent a promising and versatile approach to improving the therapeutic potential of drugs and nutraceuticals by enhancing their bioavailability and efficacy without contributing intrinsic pharmacological effects. Their diverse mechanisms of action—ranging from enzyme inhibition and efflux modulation to permeability enhancement and half-life prolongation—highlight their importance in both pharmacokinetic and pharmacodynamic optimization. Natural phytochemicals such as piperine, quercetin, glycyrrhizin, and ginsenosides, along with synthetic agents like surfactants, have demonstrated wide applicability across therapeutic areas, including infectious diseases, oncology, cardiovascular disorders, and inflammatory conditions. The ability of bioenhancers to reduce drug dosage, minimize side effects, and revive abandoned compounds with poor pharmacokinetic profiles underscores their clinical and pharmaceutical significance. Moreover, their integration into novel formulations such as nanoparticles, liposomes, and transdermal systems expands their utility in modern drug delivery. As research continues to explore new bioenhancers and refine their mechanisms, these agents hold substantial potential in shaping future strategies for drug discovery, development, and personalized medicine.

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