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Reviewing Bioenhancers in Traditional Indian Medicine: Exploring their Potential Mechanisms and Applications

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Abstract

Background: Natural bioenhancer is a natural substance that can improve the effectiveness and absorption of a drug or nutrient when combined with it, without displaying any typical pharmacological activity at the dosage used. By using natural bioenhancers, the required dose can be reduced, the treatment duration shortened, and the recovery rate increased. The main mechanisms underlying phyto-bioenhancers involve influencing drug absorption, such as affecting solubility, drug efflux, and transport proteins, increasing permeability in the gastrointestinal system, and affecting drug metabolism by inhibiting or inducing drug metabolizing enzymes and producing a thermogenic effect. This study explores the concept ,potential mechanisms and applications of bioenhancers in traditional Indian medicine, particularly Ayurveda.

Methods: The review will likely discuss relevant scientific literature on bioenhancers in traditional Indian medicine, focusing on their mechanisms of action and documented applications. It might also explore historical references to bioenhancers in Ayurvedic texts like Charaka Samhita and SushrutaSamhitafor references to "Anupana" and "Yogavahi," terms associated with bioenhancement. It further investigates the categorization of bioenhancers and the use of examples like piperine (black pepper) and "Trikatu" (ginger, black pepper, long pepper) in Ayurvedic practice.

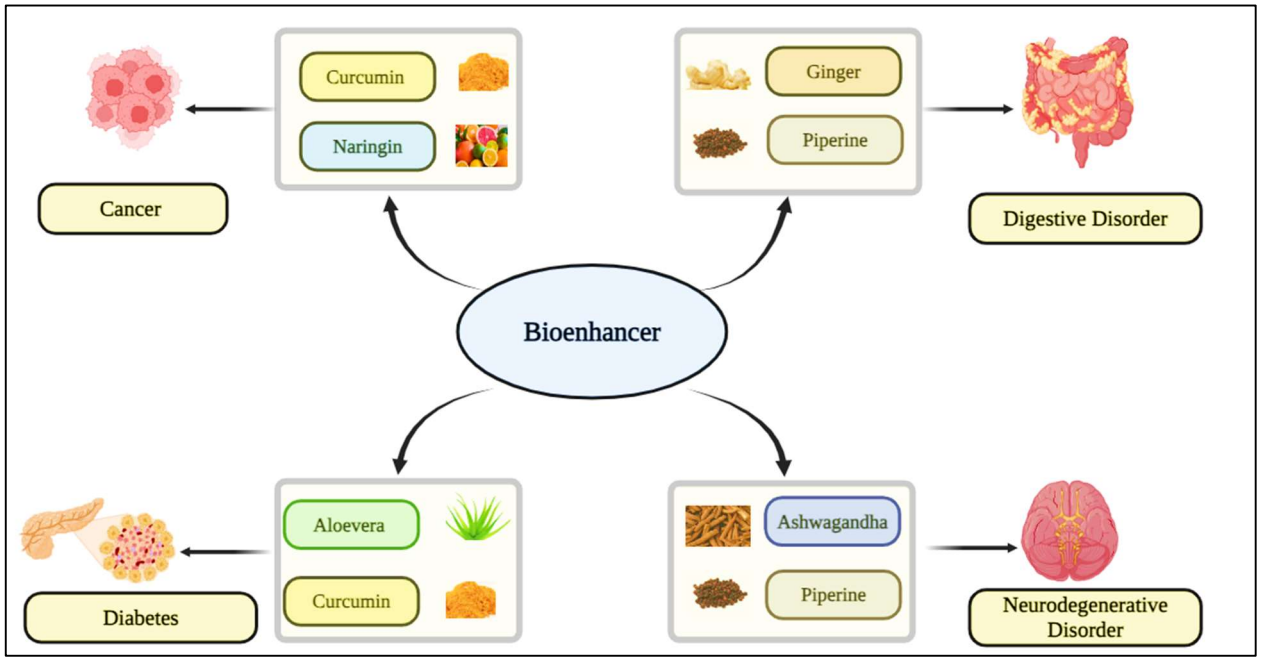
Results: The research demonstrates a long-standing tradition of using bioenhancers in Ayurveda. Historical understanding was based on empirical evidence, while contemporary research is unveiling the scientific mechanisms behind their efficacy.

Conclusion: The study highlights the significance of bioenhancers in traditional Indian medicine and emphasizes the importance of scientific inquiry for validating and integrating these practices into modern healthcare. The potential of

bioenhancers in traditional Indian medicine and pave the way for further research on their mechanisms and applications in modern healthcare.

Keywords Bioenhancers, Biomarkers, Classical complementary and alternative medicine, Pharmaceutical agents

Graphical Abstract



Introduction

Over the past two decades, there has been a growing interest among major pharmaceutical companies in therapeutic botanicals. This is the result of increased public and scientific interest and awareness regarding medicinal flora. The estimated valuation of the worldwide commerce of medicinal plants and their products by 2050 is $5 trillion, with China and India appearing as significant participants in this market.[1]Herbal treatments and a holistic approach to health have been known for a long time in traditional Indian medicine, which includes systems like Ayurveda and Siddha. [2]One of the key components of these systems, known as "bioenhancers," is gaining attention in both conventional and modern medicine.[3,4]The effectiveness of medications, minerals, and herbal therapies is significantly impacted by bioenhancers because they facilitate the body's absorption and utilization of bioactive substances.[4]In the field of traditional Indian medicine, bioenhancers are extremely significant. Since ancient times, these systems have developed, utilizing nature's bountiful resources to support the repair and overall well-being of people's bodily, mental, and spiritual elements.[5]Ayurveda is a traditional medicine that dates back over 5,000 years. It emphasizes the need of striking a balance between a person's constitution and their environment. [6]Often, Ayurvedic treatments involve the use of herbal medicines that are tailored to the unique constitution of each patient, or "prakriti." These formulations have been created to address particular disorders as well as to support general health and vitality.[7]There are various factors that can influence the efficacy of herbal medicines and therapeutic substances, including variances in human anatomy, metabolic rates, and absorption capacities. By functioning as catalysts, bioenhancers play a pivotal role in enhancing the bioavailability of bioactive compounds, hence promoting their optimal absorption, distribution, and metabolism.[8]As a result, this occurrence increases the effectiveness of other chemicals and traditional Indian remedies as treatments.

The historical origins of bioenhancers in traditional Indian medicine can be attributed to ancient literary sources, namely the Charaka Samhita and Sushruta Samhita, which are considered fundamental writings in the field of Ayurveda. The aforementioned books provided an introduction to the notion of "Anupana," which pertains to substances employed for the purpose of augmenting the therapeutic effectiveness of medicinal plants and chemicals.[9] Moreover, the authors provided a comprehensive explanation of the concept of "Yogavahi," which pertains to substances that effectively augment the absorption and distribution of pharmaceutical agents within the body. [10] Throughout the course of history, Ayurveda has undertaken the task of classifying bioenhancers into distinct categories, taking into consideration their specific activities and impacts on the human body.[11] One notable instance involves the compound piperine, which is obtained from black pepper. Piperine has garnered recognition due to its capacity to enhance the assimilation of several nutrients and medications. Increasing the enzyme activity in charge of drug metabolism produces this effect.[12]The presence of this ingredient is no less important both in modern drug formulations as well as in ancient Ayurveda medications for it can be used to fight against inflammations and oxidative stress.[13]The characteristic of "Trikatu," the combination of ginger, black pepper, and long pepper, is the widely used Ayurvedic drug that increases the effect of the remedy. Ginger has been shown to be good for the digestive system, and contains anti-inflammatory properties. Such traits improve the absorption of nutrients and contribute to the entire beneficially acting process of herbal remedies.[14]Through examining the underlying mechanisms of bioenhancers, scientific research from the present day has started to close the gap between traditional Indian medicine and science. Though their use has historically been based on established empirical knowledge, more recent studies are shedding light on the complex scientific processes underlying bioenhancers' effectiveness.[15]To validate and integrate traditional practices into modern healthcare, scientific research is essential.

Origins and Development of Bioenhancers in Indian Medicine

The origins of bioenhancers, referred to as "Yogvahi" in Indian Traditional Medicine System, may be traced back to written evidence from 1929. During this time, Bose presented their findings on the ability of bioenhancers to enhance the antihistaminic qualities of Vasaka, a herbal cure.[16] Nevertheless, a significant milestone in the identification of bioenhancers was achieved in 1979 by C. K. Atal at the Regional Research Laboratory, Jammu. The emphasis placed by Atal on Trikatu, a combination comprising black pepper, long pepper, and ginger that is extensively utilized in Indian Traditional Medicine System, resulted in a significant realization. During his investigation of the elements of *Piper longum*, Atal made the discovery of piperine, a very effective bioenhancer that enhances the bioavailability of several pharmaceuticals.[3] The identification of piperine's exceptional capacity to boost the effectiveness of drugs within the framework of Indian Traditional Medicine System played a pivotal role in the establishment of the term "bioenhancer.[17]Biological membranes pose significant barrier to the absorption of molecules, with solubility and molecular size being key influencing factors. Compounds characterized by inadequate lipid solubility or inappropriate sizes frequently face obstacles in the process of absorption, resulting in restricted bioavailability.[18] Bioenhancers are substances that provide a solution by facilitating improved membrane penetration. These substances exhibit interactions with cellular membranes, overcoming challenges encountered by molecules possessing less than ideal characteristics, thereby enhancing their rates of absorption and total bioavailability in the organism.[19]

The junction of old Ayurvedic knowledge and modern scientific investigation is seen in recent advancements in pharmaceutical research, as demonstrated by the creation of "Risorine" by Candida Pharma. The tuberculosis treatment regimen involving the combination of rifampicin and isoniazid is enhanced by the inclusion of piperine in Risorine, which acts as a bioenhancer.[19] Piperine, derived from the *Piper nigrum* plant often known as black pepper, demonstrates the capacity to substantially enhance the bioavailability of pharmaceutical substances, hence potentially amplifying their therapeutic efficacy within the human body.[16]The use of historical information and modern scientific research together shows the good effects of working together across different fields in healthcare, which makes medicines work better and improves people's overall health.

Common Bioenhancers in Indian Traditional Medicine System and Other Traditional Systems

Bioenhancers from Indian Traditional Medicine System are known for improving the absorption and effectiveness of drugs. These bioenhancers have found use in other ancient medical systems, showing that their basic ideas are similar.[3]Piperine that is mostly present in *Piper longum* in Indian Traditional Medicine System, and in Black Pepper in Traditional Chinese Medicine (TCM), exhibits case enhancing property which helps in the enhancement of the therapeutic ingredients. Extensive scientific research has been performed on piperine, the most vital substance in the *Piper* longum, because of its deep involvement in the enhanced absorption and bioavailability of many pharmaceuticals and essential nutrients.[20]The way this medication functions is controlled by blocking the actions of enzymes that aid in the liver's drug breakdown. This inhibits the opening of blood vessels, increasing the amount of medications that enter the body through the bloodstream.[21]On the other hand, black pepper and piperine, which is found in spices, are both used in Traditional Chinese Medicine to help drugs work better. Piperine and other parts that help the body take drugs better, making the drugs stronger, are being studied. [22]Piperine, which is found in both Piper longum and black pepper, has bio-enhancing properties that make traditional medicine in those countries very important because it accelerates the healing effects of other drugs.

The botanical name for this ginger is *Zingiber officinale,* and it is used for many purposes, one of which is as a bioenhancer.[23]The characteristic appears similarly from the perspectives of TAM and the Indian Traditional Medical System. It is well known that ginger increases the potency and absorption of other botanicals and conventional medications.[24]By combining them, Ayurvedic practitioners take use of ginger's ability to improve the performance and absorption of other medications.[23]In Traditional Arabic Medicine, ginger is a multifunctional booster that helps ensure that medications are absorbed as effectively as possible, improving their effectiveness. Ginger's presence in formulations throughout traditional systems indicates that its bioenhancing properties are accepted across cultural boundaries and that it is valued as a catalyst for increased absorption and better efficacy of medical therapies.[24]

The traditional Chinese and Indian medical systems acknowledge ashwagandha (Withania somnifera) and related herbs as bioenhancers.[25]ell-known in both Traditional Chinese and Indian medicine, ashwagandha is said to boost the bioavailability of medicinal ingredients, increasing their potency when taken as directed.[26]Bioenhancers are used in traditional medicine, which shows how ancient knowledge and modern science knowledge are coming together. Traditional knowledge and scientific studies that back up the bioenhancing effects of these herbs are in line with each other, proving that they play a key role in improving therapeutic results. The use of bioenhancers in various traditional methods shows that people from different cultures share a common goal of making medicinal compounds work better.

Table 1: A summary of natural bioenhancers and their major mechanisms and uses

S.No.	Bioenhancer	Biological Name	Mechanism of Action	Uses	References
1.	Aloe vera	*Aloe barbadensis*	Metabolism inhibition; tight junction modulation, Local mucosal tissue modulation	Anticancer, antioxidant, antidiabetic, antihyperlipidemic, skin protection, and digestive disease protection	272829
2.	Ashwagandha	*Withania somnifera*	Stimulates the immune system by enhancing the	Reduces anxiety, boosts cognitive abilities, enhances	3031

			proliferation of T lymphocytes and increasing NK cell activity	exercise performance, increases sperm health and testosterone levels, improves sleep quality, reduces blood sugar levels, improves arthritis symptoms	
3.	Amla	*Phyllanthus emblica*	Inhibiting the NF-κB signalling pathway and enhancing the activities of NK cells and cytotoxic T lymphocytes	antipyretic, analgesic, antitussive, antiatherogenic, adaptogenic, cardioprotective, gastroprotective, antianemia, antihypercholesterolemia, wound healing, antidiarrheal, antiatherosclerotic, hepatoprotective, nephroprotective, and neuroprotective properties	[32,33]
4.	Curcumin	*Curcuma longa Linn*	Efflux transporter (P-gp) inhibition; metabolism (CYP3A4) inhibition	Multiple myeloma, pancreatic cancer, colon cancer, mastitis myelodysplastic syndromes, psoriasis, alzheimer's disease, diabetic nephropathy, periodontal disease, recurrent apthous stomatitis	[34,35]
5.	Ginger	*Zingiber officinale Roscoe*	Ginger aids absorption by modulating gastrointestinal function	ginger improved lipid profiles and benefited the glucose control, insulin sensitivity, glycosylated hemoglobin of type 2 diabetes mellitus, arthritis, gastric dysfunction, and cancers	[36]
6.	Gokhru	*Tribulus terrestris*	Local mucosal tissue modulation	Aphrodisiac activity and curative effects, hepatoprotective, antiulcer, anti-inflammatory, anti-bacterial, antioxidant, anti-	[37, 38]

				hyperlipidemic, and nephroprotective	
7.	Naringin	Plant (grapefruit, apple, onion, tea)	Efflux transporter (P-gp) inhibition; metabolism (CYP3A4) inhibition	Antioxidant anti-inflammatory, anti-apoptotic, anti-atherosclerotic, neuroprotective, anti-psychotic, anti-asthmatic, anti-diabetic, hepatoprotective, anti-tussive, cardioprotective, and anti-obesity activity	[39], [40]
8.	Piperine	*Piper longum, Piper nigrum*	Local mucosal tissue modulation; thermogenic activity, Decreased elimination (gastrointestinal transit inhibition; gastric emptying inhibition), Piperine's methylenedioxyphenyl ring helps to inhibit drug-metabolising enzymes such as CYP 450 and UDP glucuronyl transferase. P-gp is also inhibited, causing drug efflux from enterocytes	Antioxidant, anticancer, anti-inflammatory, antihypertensive, hepatoprotective, neuroprotective and enhancing bioavailability and fertility-related activities	[41],[42], [43], [12]
9.	Quercetin	Citrus fruits (lemon, orange , grapefruits)	Efflux transporter (P-gp) inhibition; metabolism (CYP3A) inhibition, activating the expression of PI3K/PKB signalling pathway-related genes	Reducing LPS-induced cardiac abnormalities in mice,Anti-Inflammatory and Immunosuppressive effects, anticancer, regulates glucose metabolism, reduces oxidative damage, and protective effect on ascorbic acid therapy.	[44], [45], [46]
10.	Resveratrol	*Vitis vinifera* (grape skin)	Efflux transporter (P-gp, MRP-2) inhibition; reduced elimination; renal uptake transporter	Antioxidant, cardioprotective, neuroprotective, anti-inflammatory and anticancer activities	[47], [48]

			(OAT1, OAT3) inhibition		

Mechanisms of Action

Herbal bioenhancers exert their effects through various mechanisms of action. Various herbal bioenhancers may exhibit similar or distinct methods of action. The bioavailability of nutraceuticals is enhanced through their interaction with the gastrointestinal system, which facilitates absorption. Conversely, the bioavailability of pharmaceuticals is increased through their interaction with the drug metabolic process.[23] Herbal bioenhancers exhibit a wide range of methods to enhance the efficacy of drugs. The strategies involve the reduction of hydrochloric acid output, enhancement of gastrointestinal blood supply, and modification of gastrointestinal transit, gastric emptying time, and intestinal motility. These enhancers allow improved drug absorption by changing the permeability of the epithelial cell membrane in the gastrointestinal system. Moreover, these substances demonstrate cholagogic actions, possess bioenergetic and thermogenic characteristics, and notably, they impede first-pass metabolism while suppressing drug-metabolizing enzymes. [16]Oral bioenhancers dramatically lower rat liver UDP-glucuronyltransferase and arylhydrocarbon hydroxylase (AHH) activity. Oral bioenhancers dramatically lower rat liver UDP-glucuronyltransferase and arylhydrocarbon hydroxylase (AHH) activity.[3] Additionally, several bioenhancers can alter the rates of glucuronidation by preventing transferase activity and lowering endogenous UDP-glucuronic acid levels and also have the ability to inhibit human P-glycoprotein and CYP3A4.[49] Dietary bioenhancers like piperine may influence plasma concentrations of P-glycoprotein and CYP3A4 substrates in humans, especially when these drugs are taken orally, since both proteins are produced in enterocytes and hepatocytes and play a significant role in the first-pass elimination of many drugs. It can inhibit or induce several metabolizing enzymes, including CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4, and many more. Thus, bioenhancers will affect the majority of medicines metabolized by these enzymes.[50] Bioenhancers' precise action mechanisms are still under investigation.

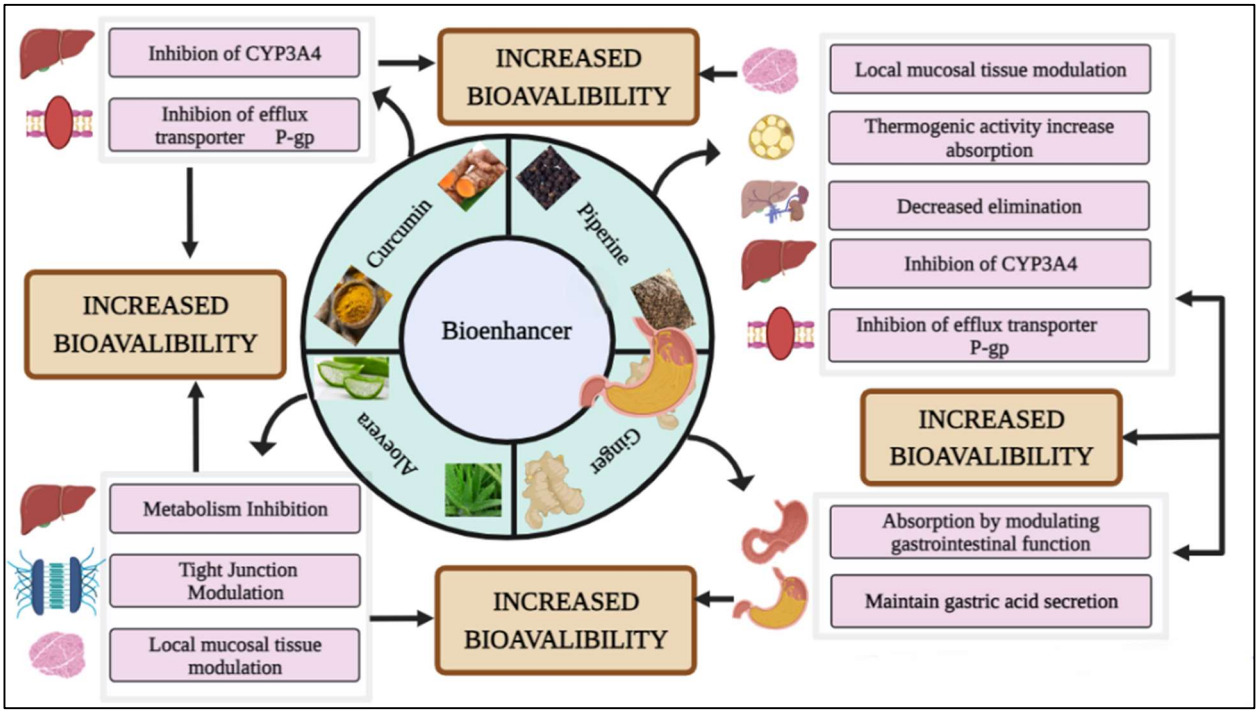


Figure1: Potential mechanism of action of selected bioenhancers

Additional proposed methods include boosting medication absorption by dilatation of the gastrointestinal tract (GIT) and functioning as receptors for drug molecules; increasing the responsiveness of target receptors to pharmaceuticals; and modulating the dynamics of cell membranes to enhance drug transport across cell membranes.[42]Enhancing the solubility of medications with limited solubility is a pivotal undertaking in augmenting their absorption and bioavailability, facilitated by the use of bioenhancers. Bioenhancers effectively address the challenge of limited solubility of these chemicals in human fluids, hence improving their absorption.[51] Upon ingestion, these enhancers exert their effects by altering the structures or habitats of the drug by the modification of its physicochemical qualities via the inclusion of certain chemicals or through interactions with other substances.[52]To improve solubility in physiological fluids, two strategies can be used: complex formation or molecular modifications that increase dispersibility.[53]Furthermore, it's crucial to remember that pharmaceutical compounds might become more soluble in water with the help of bioenhancers like piperine. This enhances their bioavailability by facilitating the body's absorption.[54]It's also important to remember that bioenhancers have the ability to alter the environment in the digestive tract, which implies that by altering the surfactant properties or pH levels of digestive fluids, they may be able to alter their solubility. Combining bioenhancers improves the solubility of medications. This facilitates the body's absorption of medications and their therapeutic application.[55]Circulatory system-influencing bioenhancers are essential for optimizing the effectiveness of drug delivery to specific tissues. These enhancers maximize the dispersion and transportation of medications or chemicals to their targeted sites of activity by promoting enhanced blood circulation in certain places.[4]These therapies improve the administration of therapeutic medications by raising tissue perfusion, which speeds up and increases the body's distribution of those medications. Improved blood circulation makes it easier for blood to be delivered to particular tissues or organs, which in turn promotes efficient waste product clearance and ensures that blood is always supplied with oxygen.[56] Several bioenhancers have been found to possess vasodilatory effects, which result in the dilation of blood vessels and thereby enhance blood circulation.[57] Illustrative instances comprise chemicals found in botanicals such as *Ginkgo biloba*, which facilitate the augmentation of blood circulation to peripheral tissues, hence intensifying the administration and effectiveness of medicinal drugs.[58] Furthermore, it is notable that these enhancers have the potential to exert a favourable impact on microcirculation. This is achieved by enhancing capillary perfusion and allowing the entry of drugs into tissues that would otherwise have limited accessibility. In general, the utilisation of bioenhancers facilitates the optimisation of blood circulation, accelerating the administration of drugs and perhaps reducing the time it takes for the desired effects to occur while also improving the effectiveness of the treatment.

Indian Traditional Medicine (ITM) and Bioenhancers

Indian Traditional Medicine (ITM) stresses taking care of your health and wellness in a complete way. The idea is that a person's physical, mental, and social health should be in balance with their surroundings. As part of ITM, bioenhancers are used.[59] These are substances or compounds that make other substances or drugs more bioavailable and effective. In the body, they help make the absorption, distribution, metabolism, and elimination (ADME) of active substances better.

Chyawanprash

Using a traditional Ayurvedic recipe, the ancient Indian composition known as Chyawanprash—a polyherbal jam—is made with a variety of herbs, herbal extracts, and processed minerals. The supplement CP has been known for decades, and many experts consider it necessary for health. Long recognized as a medicinal herb with anti-aging and immune-boosting properties, chyawanprash has a long history of usage as a dietary supplement. [60]An antioxidant paste called chyawanprash is made by combining about fifty different herbs and spices in a harmonious way. Chyawanprash is an Ayurvedic formulation that, according to its consistency and method of administration, belongs to the class of Awaleha, which means electuaries or herbal jams.[61]Piperine, a bioenhancer derived from black pepper or long pepper, is an essential component in chyawanprash compositions because it increases the bioavailability and absorption of the herbs' many active ingredients.[62] Inhibiting specific enzymes that metabolize these molecules is how piperine works; as a result,

these substances remain in the bloodstream for longer.[12] The herbal components in Chyawanprash have the potential to be more effectively absorbed, which could increase their therapeutic efficacy and make better use of their health-enhancing characteristics.[63]

Triphala Churna

The three fruits *Emblica officinalis* (Amla), *Terminalia bellirica* (Bibhitaki), and *Terminalia chebula* (Haritaki) are mixed in equal parts to make Triphala Churna, a highly esteemed composition in conventional Ayurvedic treatment.[64]Wide variety of bioactive substances, this combination provides a range of health benefits. Triphala recipes like Anu-Phala call for piperine, a bioenhancer derived from long pepper (*Piper longum*), to help the body absorb the medicinal ingredients more effectively.[65]The use of triphala churna is most commonly explained by its numerous, powerful effects on the digestive tract. Its ability to manage constipation, facilitate digestion, and promote general gastrointestinal health is the reason for its widespread use. Moreover, triphala's strong antioxidant content is well-known for its ability to scavenge free radicals and shield cells from oxidative stress-related damage. Because of its antioxidant content and all-encompassing support for the digestive system, triphala churna is a component of traditional medicine that aids in preserving overall wellness and digestive health.[66]

Guduchi Preparation

The medicinal herb guduchi, (associated with scientific term *Tinospora cordifolia*), is really potent because it supports the immune system in many possible ways. The number of potent bioactive compounds present in the herb Guduchi is remarkable. These are examples of salts, glycosides, alkaloids, diterpene lactones, and polysaccharides.[67]Some of the preparations such as Kofol require bioenhancers like curcumin and piperine, which are derived from turmeric and black pepper, in order to increase its efficacy. These bioenhancers help in better absorption and utilization of guduchi's nutritious components by the body. Guduchi enhance immunity system by increasing resistance to diseases through reducing fever because it has known antipyretic and immunomodulatory effects. It is a must-have item in traditional medicine that supports overall health due to its broad spectrum actions on antioxidant, anti-inflammatory and adaptogenic characteristics.[68]

Bioenhancer in marketed formulation

Bioenhancers included in commercially available formulations have the capacity to augment the absorption of active constituents within the body, hence amplifying their efficacy. They enhance the bioavailability of substances, hence optimizing their medicinal efficacy. These enhancers play a role in improving absorption, hence enhancing the body's utilization of the components in a more efficient manner.[16] Pharmaceuticals and supplements incorporate them into their compositions in order to enhance their effectiveness. Bioenhancers included in commercially available goods have the ability to augment the efficacy and advantageous effects of their primary constituents.[3]**Arsohills Tablets**

Herbal Hills Arsohills Tablets are formulated with a powerful combination of natural substances that are known to alleviate heat-related bowel issues, fissures, and piles.These components include Suran, Senna, Triphala, Nagkesar, Vidang, Sharpunkha, Shuddha Tankan, and Chitrak. This hemorrhoidal mixture helps with smoother bowel movements and prevents piles from returning by reducing inflammation, stopping bleeding, and alleviating pain. These tablets provide a natural, non-toxic substitute for pharmaceuticals and harsh chemicals by relieving pain and burning in the rectal area. Consistent consumption controls hepatic functions, which in turn promotes efficient defecation, and softens and lubricates stool. Hemorrhoidal issues can be effectively managed with the use of Herbal Hills Arsohills Tablets, which offer a complete solution that promotes long-term comfort with no adverse effects.

Herbal Hills Proscarehills Tablets

Herbal hills proscarehills tablets is an ayurvedic medicine that is primarily used for the treatment of prostatitis. Herbal hills proscarehills tablets is manufactured by Isha Agro Developers pvt. Ltd. The key ingredients of herbal hills proscarehills tablets are gokshura, ashwagandha, guggul, punarnava, varuna.Gokshura and Punarnava help with fever, pain and swelling, as well as expel excess water from the body, lower blood pressure and detoxify. They also prevent

the formation of kidney stones. Ashwagandha reduces inflammation after injury and helps control inflammation. Guggulu also reduces inflammation and can fight infections like sepsis. Varun is anti-inflammatory, prevents kidney stones, and reduces their symptoms.

Trimohills Tablets

Trimohills (Natural Weight Loss Supplements) is an Ayurvedic formulation of Shuddha Guggul, Triphala, Trikatu, Trimad, and Vrikshamla. It may have antioxidant, detoxifying, anti-lipidemic and digestive properties. Triphala may promote healthy digestion and may act as a natural cleanser. It may help in keeping the stomach clean, promote metabolism and may provide strength to rectal muscles. Consequently, it may help to reduce the weight, combating gastric ulcers and urinary tract infections. Guggul may help in lowering the lipid levels and fats in the body, thereby facilitating the weight loss process. Vrikshamla may help in preventing the formation of body fats.

Table 2:

S. No.	Patent No.	Title	Bioenhancer	Conclusion
1.	CN112243383A	Pharmaceutical preparation	Piperine	Piperine used with anti-tuberculosis drug to treat tuberculosis
2.	US20120058208A1	Synergistic Composition for Enhancing Bioavailability of Curcumin	Ginger, and curcumin	Ginger and vanilla extract with curcumin to increase the bioavailability of curcumin and inhibiting tumor growth.
3.	WO2003049753A1	Bioavailability enhancing activity of *zingiber officinale* linn and its extracts/fractions thereof	Ginger and piperine	Synergistic bio-enhancing composition with ginger and piperine optimizes nutrient absorption and efficacy
4.	US20220218781A1	Composition for enhancement of bioavailability of phytochemicals and process for preparation thereof	Aloe vera, curcumin, garlic	This innovative composition enhances phytochemical dispersion and bioavailability using plant-derived bio-enhancers effectively

5.	US20170348209A1	Compositions of resveratrol and methods for their use and manufacture	Resveratrol	Resveratrol-based formulations amplify bioactivity, enhancing health benefits for various conditions and disorders effectively.

Potential Applications

Cancer Treatment

Bioenhancers such as curcumin derived from turmeric, piperine obtained from black pepper, and quercetin sourced from onions demonstrate encouraging potential in terms of their anticancer activities.[69] Curcumin, a well-known compound recognized for its antioxidant and anti-inflammatory properties, exhibits promise in augmenting the effectiveness of chemotherapy by the potentiation of cytotoxic effects induced by medicines such as paclitaxel and 5-fluorouracil (5-FU).[70]Furthermore, it has the potential to mitigate drug resistance in cancer cells through the modulation of biological pathways, hence enhancing their susceptibility to therapeutic interventions. The anti-angiogenic properties of this substance hinder the process of neovascularization, hence inhibiting the growth and spread of tumors.[71]

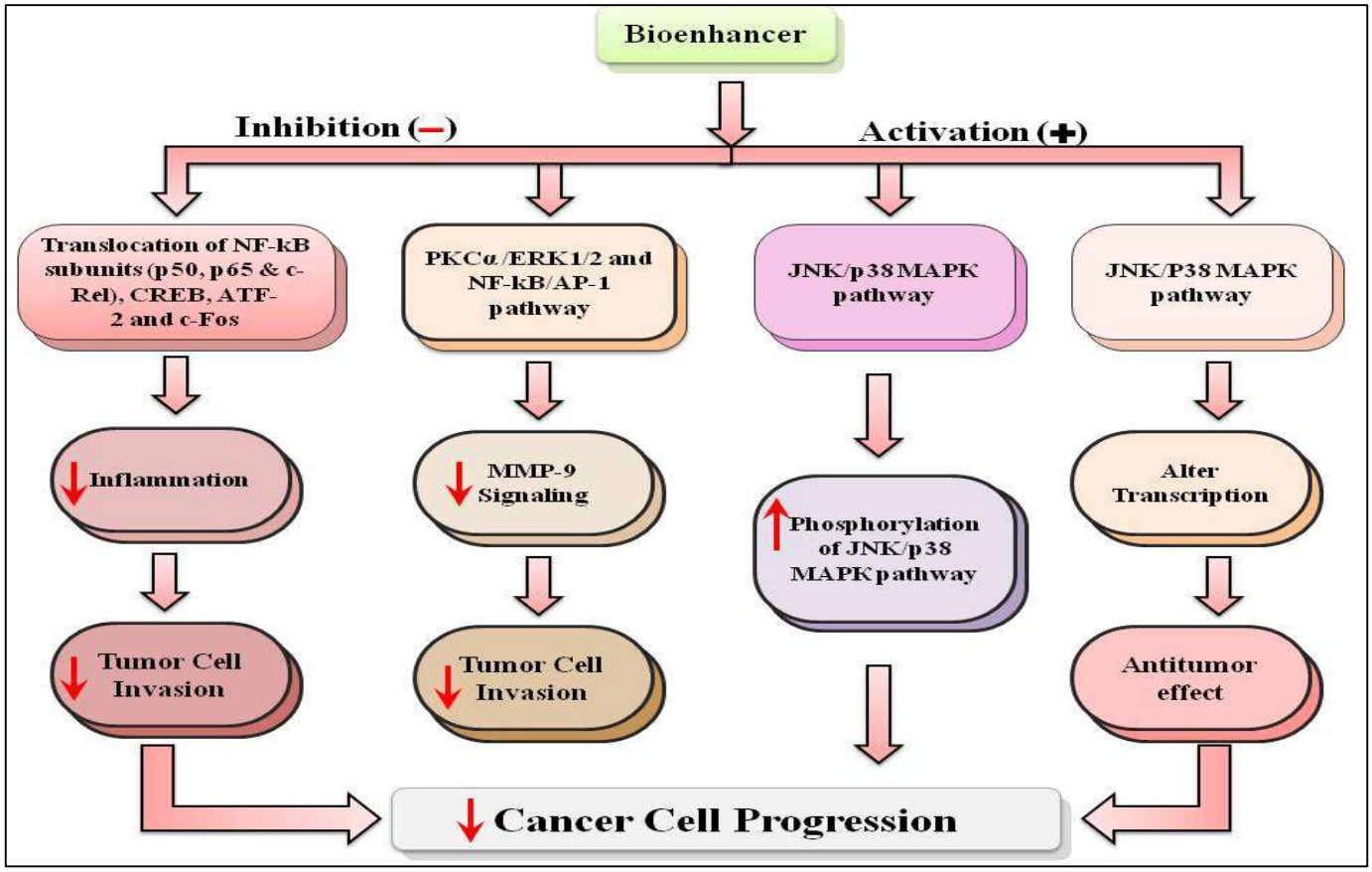


Figure 2: Role of bioenhancers in cancer treatment

Piperine, a compound recognized for its capacity to boost the bioavailability of substances, has been found to greatly increase the absorption of curcumin and improve the uptake of specific chemotherapeutic drugs.[16] Quercetin, a plant

flavonoid present in fresh fruits, vegetables, and citrus fruits, possesses anti-cancer characteristics by impeding the growth, invasion, and spread of tumours. Multiple studies have elucidated the anti-cancer properties of quercetin, which exert their effects by modulating various signalling pathways within cancer cells. The pathways implicated in this process encompass apoptotic, p53, NF-κB, MAPK, JAK/STAT, PI3K/AKT, and Wnt/β-catenin pathways. Quercetin not only regulates these pathways, but also modulates the activity of oncogenic and tumour suppressor non-coding RNAs (ncRNAs).[72] The presence of healthcare specialists overseeing the use of medical interventions is essential in order to optimize their advantages and uphold the well-being of patients, as well as to guarantee the efficacy of therapy.

Digestive disorder

Bioenhancers such as ginger, black pepper, and long pepper are known to have significant effects on promoting digestive well-being.[55] Ginger possesses a lengthy historical background in its ability to alleviate gastrointestinal discomfort, encompassing conditions such as indigestion, bloating, and nausea. This is achieved through the stimulation of digestive enzymes and the facilitation of efficient digestion. The possible anti-inflammatory qualities of this substance have the ability to provide relief to the digestive tract, hence offering potential benefits for those with disorders such as gastritis or inflammatory bowel diseases.[73] The consumption of black pepper has been found to have a positive impact on digestive function. This is achieved by the stimulation of enzyme secretion, which aids in the digestion of food.[74]Additionally, the presence of piperine in black pepper has the ability to boost nutrient absorption, making it a potentially beneficial dietary addition for those with malabsorption disorders.[75] Long pepper, renowned for its potential to enhance digestion and alleviate digestive discomfort, is purported to exhibit anti-flatulent characteristics by mitigating the development of gas and alleviating bloating, which are prevalent manifestations in several digestive illnesses.[76] Bioenhancers have the potential to mitigate symptoms commonly associated with indigestion or dyspepsia, facilitate more efficient digestion in those diagnosed with irritable bowel syndrome (IBS), and assist in the absorption of nutrients in individuals affected by malabsorption disorders. [77]Nevertheless, it is imperative to provide oversight when utilizing these substances, guaranteeing the administration of suitable quantities and compositions that are specifically customized to meet the unique requirements of each individual.

Diabetes Management

Bioenhancers like fenugreek and bitter melon may help the body's metabolism of glucose, which could lead to new ways to treat diabetes, especially when used with regular medicines. Because they have a lot of dietary fiber, trigonelline, and galactomannan, fenugreek seeds may help control blood sugar by making it take longer for carbohydrates to be broken down and absorbed.[787980] Studies show that fenugreek can make insulin work better, which could help cells use glucose more efficiently and lower insulin resistance.[78] Meanwhile, bitter melon has chemicals in it like charantin, vicine, and polypeptide-p that work like insulin. This means that it may lower blood sugar levels and help cells take in more glucose.[79] These bioenhancers show potential in controlling blood sugar, which is very important for managing diabetes. On their own, fenugreek and bitter melon are not intended to substitute for diabetes medication; instead, they may function better in combination with other treatments by increasing insulin and glucose sensitivity in the body. Incorporating fenugreek or bitter melon into a healthy diet coupled with exercise and changes in your lifestyle can assist balance blood sugar levels.[81]

7.4 Neurodegenrative disorders

The use of curcumin, an ingredient derived from turmeric, in the treatment of neurological conditions like Parkinson's and Alzheimer's is developing favor. This has mostly happened as a result of its recognized anti-inflammatory and neuroprotective qualities. This chemical is important because of its significant anti-inflammatory properties, which may make it a useful therapeutic treatment for inflammatory diseases. It is especially important to consider its influence on neurodegenerative diseases like Parkinson's and Alzheimer's.[82]Studies show that it can protect neurons from damage and reduce oxidative stress, two critical aspects of these specific illnesses. β-amyloid plaque deposition is closely linked to neuronal damage in Alzheimer's disease, curcumin shows promise as an efficient inhibitor of this process.[83]On the other

hand, curcumin also has a ability to inhibit the formation of pathological tau proteins. Thus, it lowers the adverse effects of this disease.[84]Furthermore, this method of care may potentially help improve cognitive function and memory performance in elderly people who are predicted to progress to develop Alzheimer's disease or have already been diagnosed with it.[85]Evaluating curcumin's potential as a neuroprotective and antioxidant drug may have an impact on dopaminergic neuron cell death. Curcumin is safe and effective, according to preliminary studies conducted on humans and animals. Therefore, more human research is crucial to advance our understanding of how to treat these complicated neurological conditions. [86]It is difficult to overstate the significance of high-quality clinical trials, where researchers should investigate the optimal dosage and long-term effects of curcuminous. Such research is obviously necessary in order to investigate curcumin as a potential drug for treating Parkinson's and Alzheimer's diseases.

Safety and Considerations

Importance of Standardized Manufacturing Processes

The same production techniques facilitates the use of bioenhancers. The main component that ensures the product is secure, consistent, and of excellent quality is standardization. Broad spectrum testing and strict quality standards meet the requirements for attaining a particular degree of therapeutic activity substance and for the removal of contaminants. To ensure that patients are protected by standardized medications, it is necessary to establish a dose that is both safe and effective and to formulate the medications regularly. [8]

Interactions

The higher concentrations of piperine, which is found in black pepper, contain vital bioenhancing characteristics, these lead to the augmentation level of many drugs, such as prescription drugs and specific minerals.This chemical works by inhibiting certain enzymes, especially those in the CYP450 enzyme family, such as CYP3A4 and CYP2E1. These enzymes are essential for the liver and intestines to properly metabolize medications. Because inhibition slows down the metabolism of medications, it might raise blood levels of such drugs, potentially intensifying their pharmacological effects.[13,87]However, as a result of the body's altered ability to absorb and eliminate certain drugs, their increased bioavailability also increases the risk of adverse reactions or toxicity.[88]Piperine may not work as well for some people when mixed with other drugs from the same class. This could be because of genetics, the amount being taken, or the medicines being used.

Dosage

The process of determining the optimal dosage for bioenhancers, which are often obtained from natural sources like plants, presents challenges because their effectiveness varies depending on a range of parameters such as growing conditions, harvesting methods, and processing procedures.[89]Piperine content in black pepper can vary depending on a variety of factors. Factors including metabolism, health status, and medical diseases increase the diversity in an individual's response to pharmaceutical dosages.[90]Hence, this may result in an environment where this one dosage may perform differently on one individual than it will perform on another person. Moreover, the transporting of drugs with bioenhancers may impact the bioavailability of them, which the digestive factors also affect the absorptions of them. As for dosage, information are provided by clinical studies, but the lack of available data, especially when it comes to different species, leads to inconsistent dosage recommendations.[16]By following the precision medicine tailored approach, the advantage is to maximize the positive outcomes, while at the same time minimizing any possible side effects, for example, when taken as a dietary supplement.[91]

Quality and Purity

Assurance about the quality and purity of bioenhancers to confirm their safety and effective use is the main requirement. The process of acquiring and extracting resources is very important. These include obtaining bioenhancers from a trustable vendors who are reputable and only sell the purest of substances in addition to following contamination free extraction methods.[92]Thorough third-party testing carried out by respectable organizations like USP or GMP certification ensures the potency, purity, and compliance with legal requirements for pollutants like heavy metals and pesticides. Standardized active ingredients are used to provide a high degree of consistency, and clear labeling with detailed information on concentrations, allergies, and additives makes it easier for consumers to make educated choices. Key factors include the appropriate storage, compliance with regulations, and adherence to rules set by health authorities. Choosing products from reputable manufacturers that promote transparency and quality assurance effectively reduces the potential risks connected with impurities or contaminants in bioenhancers.[93]

Challenges and Future Prespective

The idea of bioenhancers has proven to be extremely innovative in today's environment. Both the risk of medication resistance and the dosage of bioenhancers are decreased. The previously mentioned investigation showed a substantial decrease in the activity of UDP-glucuronyltransferase and hepatic arylhydrocarbon hydroxylase (AHH) in rats given piperine orally.Furthermore, the findings clarify how bioenhancers can modify glucuronidation rates by obstructing transferase activity and reducing endogenous UDP-glucuronic acid levels. Furthermore, their impact on drug metabolism and absorption is further highlighted by their suppression of important factors such as human P-glycoprotein and CYP3A4. In Traditional Indian medicine, researching bioenhancers is akin to finding novel ways to improve the way medications interact with our bodies. These substances have a great deal of potential to improve drug absorption and even alter how our bodies metabolize pharmaceuticals. It is very important that we increase a systematic understanding of the mechanism of actions of these bioenhancers, as well as any potential side effects or medication interactions. Determining this is critical to the safe and efficient administrations of these bioenhancers in actual medical therapies.

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