processes

MDPI

Review

Role of Natural Phytoconstituents as a Potential Bioenhancer of Anti-Cancer and Anti-Microbial Agents: Spotlight on the Mechanism of Action, Clinical Studies and Patents

Dhanalekshmi Unnikrishnan Meenakshi †, Gurpreet Kaur Narde †, Alka Ahuja *, Md Jawaid Akhtar * and Shah Alam Khan

College of Pharmacy, National University of Science and Technology, Muscat PC 130, Oman; dhanalekshmi@nu.edu.om (D.U.M.); gurpreetdrd@rediffmail.com (G.K.N.); shahalam@nu.edu.om (S.A.K.)
* Correspondence: alkaahuja@nu.edu.om (A.A.); mjawaid@nu.edu.om (M.J.A.)
† These authors contributed equally to this work.

Abstract: A drug design strategy with reduced side effects and economic feasibility is desirable for fatal diseases. Increasing the bioavailability of a drug using a bioenhancer is a smart strategy. Herbal/natural bioenhancers with no probable side effects are an ideal choice to enhance the pharmacokinetics of a therapeutic drug synergistically. The mechanism of bioenhancers relies on the retention of the drug molecule in the cell without causing any changes in the metabolic activity. Most of the herbal bioenhancers achieve this feat by inhibiting metabolic enzymes such as cytochrome P450 and Uridine 5′-diphospho-glucuronosyltransferase. The efflux pump p-glycoprotein, responsible for removal of xenobiotics, is also inhibited by herbal/natural bioenhancers. The increased bioavailability because of the higher C_{max} and t_{max} of chemotherapeutics or anti-infectious agents such as rifampicin can result in a lower drug dosage regimen. The reduction in drug dosage is directly linked to fewer side effects and economic viability. Further, there is a significant effort in clinical trials to incorporate bioenhancers in drug regimens for cancer. The role of herbal/natural bioenhancers and their potential to augment the bioavailability of therapeutics used in cancer and infectious diseases, with a focus on the mechanisms of action, clinical studies and patents, have been summarized in this review article.

Keywords: cancer; tuberculosis; bioenhancer; CYP; P-gp; C_{max}; herbal

Citation: Unnikrishnan Meenakshi, D.; Narde, G.K.; Ahuja, A.; Akhtar, M.J.; Khan, S.A. Role of Natural Phytoconstituents as a Potential Bioenhancer of Anti-Cancer and Anti-Microbial Agents: Spotlight on the Mechanism of Action, Clinical Studies and Patents. *Processes* **2024**, *12*, 2060. https://doi.org/10.3390/pr12102060

Academic Editor: Paolo Trucillo

Received: 18 August 2024
Revised: 18 September 2024
Accepted: 20 September 2024
Published: 24 September 2024

1. Introduction

The bioavailability of a drug is one of the most important factors in the design and discovery of drugs. The Code of Federal Regulations defines bioavailability as the rate and extent to which an active ingredient from the administered drug is present in a sufficient and active state at the target site [1]. The bioavailability of a drug is largely influenced by the route of administration, such as oral, skin, mucosal and intravenous routes. Although intravenous drug administration is a better choice for the 100% bioavailability of a drug molecule, a non-invasive and highly accepted option is the oral route. However, the oral route administration is marred by incomplete absorption, low bioavailability and the first-pass metabolism [2]. There are natural compounds such as piperine, caraway, curcumin, genistein, etc., that have been reported to increase the bioavailability of a drug when administered through the oral route. Such natural compounds that can increase the sustainable bioavailability of a drug at lower doses, thereby allowing it to exert therapeutic effects, but which do not have any or minimal therapeutic effects of their own, are called bioenhancers [3]. As shown in Figure 1, bioenhancers are classified based on their origin and mechanism. Bioenhancers are molecules that can increase the overall therapeutic potential/biopotential of the drug molecule: "Bio potentiation or bio enhancement refers to the phenomena of enhancing the overall occurrence of any chemical substance in the

biological fluid and systemic circulation, as well as secondary chemicals responsible for the increase in plasma drug concentration of the major component" [4].

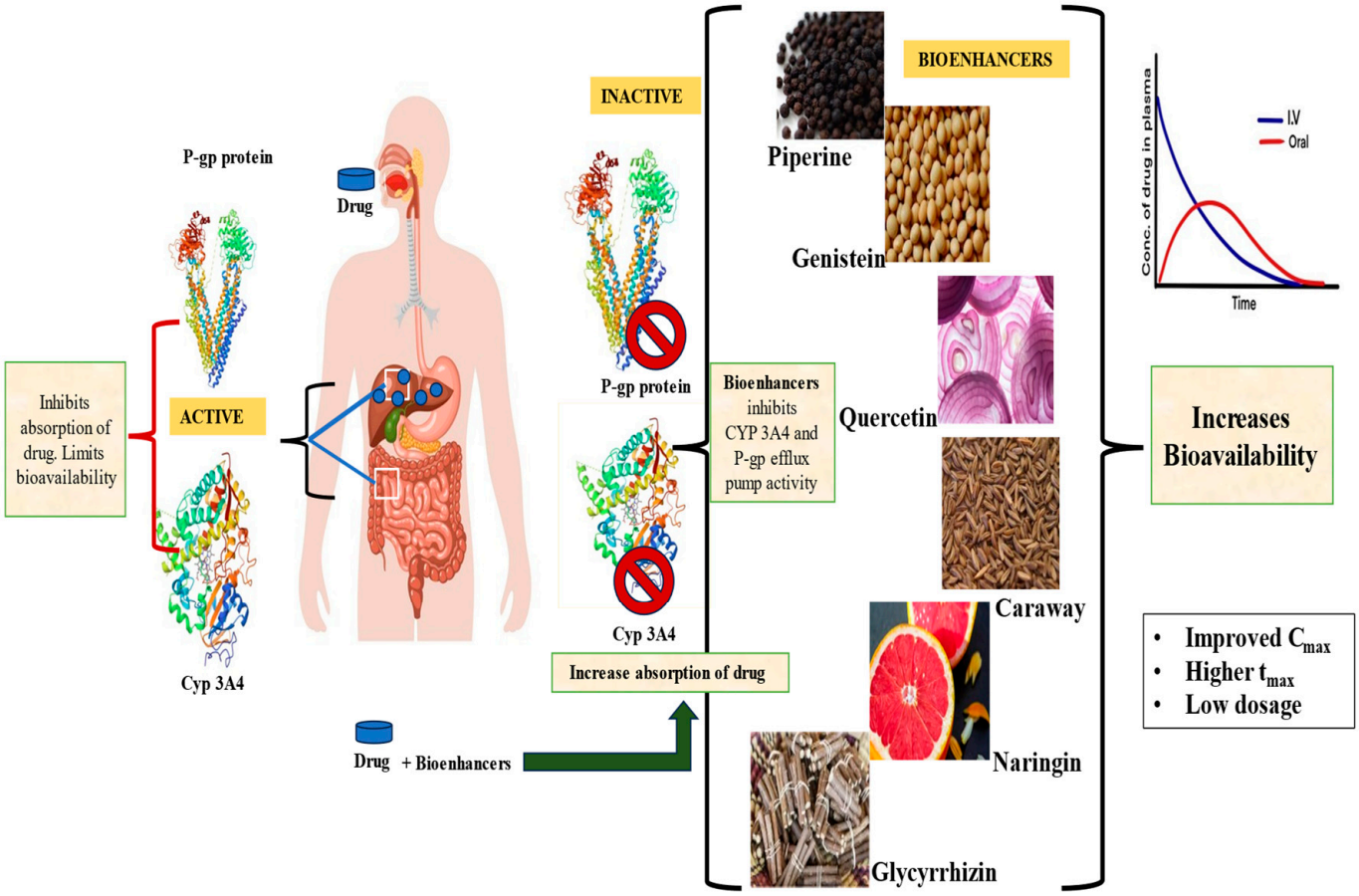

Figure 1. The two main mechanisms in the human body for the metabolism and removal of xenobiotics in humans are CYP enzymes in the liver and the P-gp efflux pump, majorly located in the intestine, respectively. Different bioenhancers of plant origin inhibit the CYP3A4 enzyme and/or P-gp protein. The result of the inhibition of the CYP3A4 enzyme and P-gp protein is an increase in the bioavailability of various drugs, proceeding with elevated C_{max} and t_{max}. There could be an overall reduction in the drug dosage as well.

Out of the many molecules being explored for the biopotentiation effect, *Piper longum* (long pepper in English or pippali in Hindi), *Piper nigrum* (black pepper in English or kali mirch in Hindi), *Zingiber officinale* (ginger in English or adrak in Hindi), sesame/til, gold/swarn bhasam, heerak bhasm and cow urine distillate have been used traditionally. In the past years, many molecules have been studied in detail for the mechanism of their biopotentiation effect, with piperine being the most explored molecule. The first report of its biopotentiation was made by Bose in 1929, where the anti-asthmatic effects of vasaka (*Adhatoda vasica*) leaves were enhanced by the addition of long pepper [5]. In recent times, piperine, quercetin, genistein, naringin, niaziridin, lysergols, capmul, sinomenine, glycyrrhizin and nitrile glycoside have been investigated for their possible biopotentiation effects along with modern medicines [6].

There has been significant research performed with a focus on different types of bioenhancers with respect to their classification, chemical properties, effects on pharmaceutical formulations and their role in the management of several diseases. Bioenhancers of a synthetic as well as plant origin have been studied. However, herbal bioenhancers not only have a remarkable ability to augment the therapeutic effects of medications used in the treatment of deadly disorders such as cancer and other infectious diseases but also

have advantages such as better absorption, safety and fewer side effects [3]. According to the World Health Organization (WHO), about one in five people develop cancer, with a staggering number of 20 million new cancer cases recorded in 2022 [7]. Infectious diseases such as HIV/AIDS, malaria, tuberculosis and others are also leading causes of death among populations. As per the reports, tuberculosis was the second deadliest infectious disease after COVID-19 in the year 2022 [8]. For such diseases and disorders, long-term therapy, affordability and medication expenses are important criteria, wherein the treatment regimen aims to have a therapeutic drug with fewer side effects. A viable strategy to reduce the cost of treatment is to reduce the therapeutic dosage of the drug, especially for deadly diseases which require long-term therapies, such as cancer and infectious diseases. The reduction in the dosage will not only beneficial in terms of the cost but also with respect to reducing the side effects due to long-term usage of the drug. A reduced therapeutic dosage will also potentially reduce the concerns about drug resistance [9]. The unutilized fraction or metabolized fraction of the drug usually results in the development of drug resistance. Hence, introducing a bioenhancer into the drug formulation is a potential strategy to address the cost, side effects and resistance to a therapeutic drug. An intriguing scenario emerges as researchers delve deeper and examine the intricate mechanisms through which herbal bioenhancers work synergistically with therapeutic agents.

Herbal bioenhancers appear to be promising acquaintances in the battle against multifactorial diseases, including cancer. They play an important role in bypassing resistance mechanisms and enhancing the effectiveness of anti-cancer medications. In the field of anti-microbial therapy, bioenhancers provide a ray of hope against the prevalence of antibiotic resistance. Herbal bioenhancers enhance the effectiveness of anti-microbial agents by inhibiting efflux pumps, preventing biofilm formation, sensing virulence factors and modifying host defense mechanisms, etc. Herbal bioenhancers exert their effect mainly due to their ability to inhibit P-gp (P-glycoprotein) and cytochrome P450 enzymes [10,11]. Bioenhancers can also have therapeutic properties of their own when administered individually. For example, the extensively studied bioenhancer piperine is known to have therapeutic properties in various diseases such as diabetes, arthritis, cancer, cardiovascular diseases, etc. [12].

Natural/herbal phytoconstituents represent a particularly compelling avenue for enhancing drug bioavailability (bioenhancement) and it allows for a lower dosage regimen without compromising the therapeutic efficacy of the pharmaceutical agents. Several ongoing clinical trials are focused on incorporating bioenhancers into therapeutic regimens, which further validates their potential role in novel treatment strategies.

The presence of a bioenhancer can dramatically change the impact of drug molecules, mainly with respect to the dosage, and this directly correlates with fewer adverse effects and improved patient compliance. This is particularly crucial in the treatment of cancer and infectious diseases, where side effects can severely impact quality of life and treatment adherence. While numerous natural bioenhancers have been identified for the enhancement of drug bioavailability, this review specifically concentrates on those bioenhancers that improve the pharmacokinetics of anti-cancer and anti-microbial agents. Therefore, this review highlights only selective bioenhancers that have demonstrated significant potential in these therapeutic areas, as there are a limited number of review reports emphasizing the effect of bioenhancers in potentiating the effects of anti-cancer and anti-microbial agents. As mentioned, herbal bioenhancers have the unique capability to amplify the therapeutic effects of drugs, and hence this review article sheds light on the biopotentiation effects of piperine, quercetin, thymoquinone, *C. cyminum*, *C. carvi*, niaziridin, glycyrrhizin, naringin and genistein as anti-cancer and anti-microbial agents. This review details the mechanisms, associated benefits, clinical studies and novel formulation approaches of natural phytoconstituents/bioenhancers in elevating the therapeutic effects of anti-cancer and anti-microbial agents.

2. Enhanced Efficiency of Therapeutic Agents: Role of Selective Bioenhancers

2.1. Anti-Cancer Agents

The impact of the addition of a bioenhancer agent along with the therapeutic drug produces a tremendous alteration in the pharmacology of the drug. As shown in Figure 2, there are natural molecules that can biopotentiate the effect of a drug used in cancer treatments. In this section, the effects of bioenhancers studied in vitro and in vivo towards the biopotentiation of anti-cancer agents are discussed.

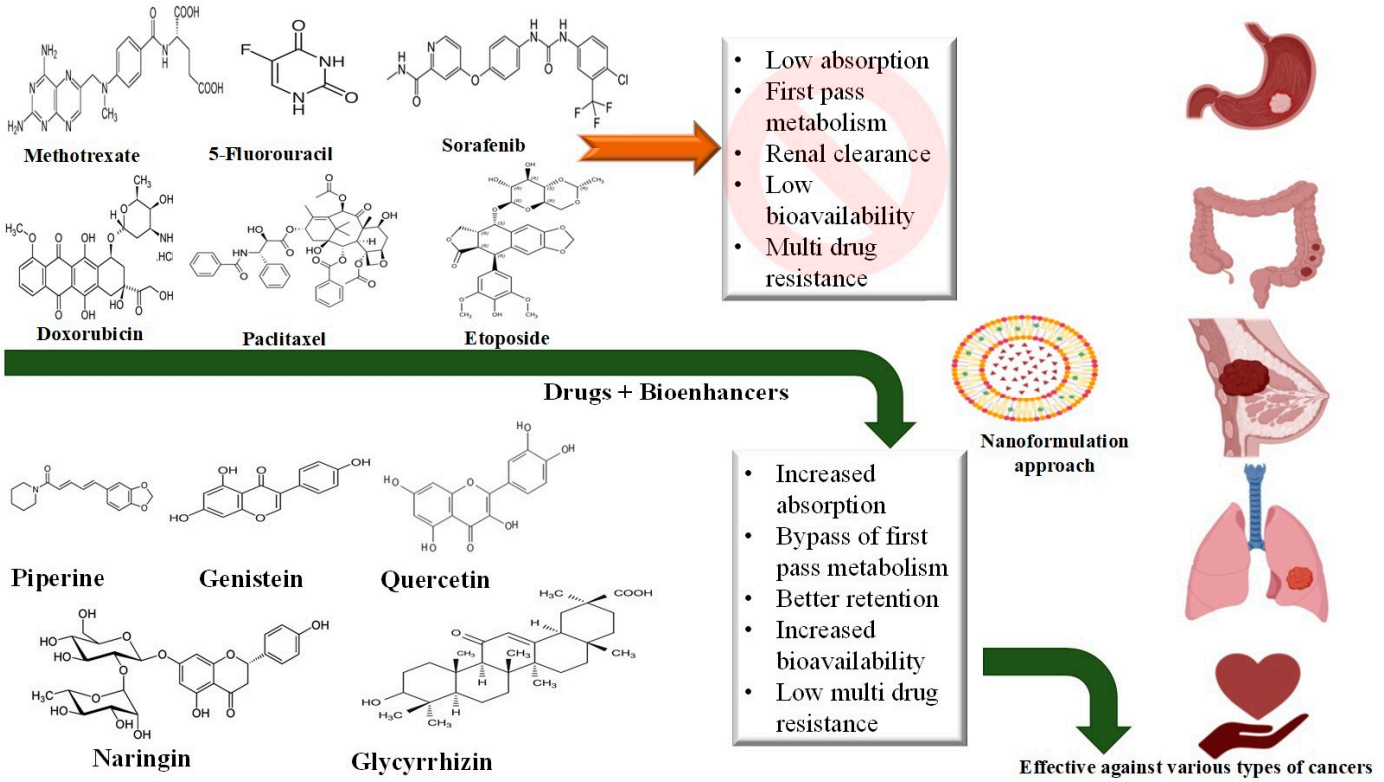

Figure 2. The resultant effect of anti-cancer drugs with bioenhancers in the treatment of various cancers, ensuing increased bioavailability.

The drug 5-fluorouracil is commonly used in the treatment of colorectal cancer. Over the past years, the increased understanding of the mechanism of action of 5-fluorouracil has led to the development of strategies to augment its anti-cancer potential. Qazi et al., 2009, reported a significant boost of 335% in the bioavailability of the anti-cancer drug 5-fluorouracil. The biopotentiation effect was obtained by using *Cuminum cyminum* (*C. cyminum*) seed extract, commonly known as caraway, which is commonly used in Asian cooking. In the same study, the bioavailability of other cancer drugs such as methotrexate (MTX), doxorubicin and cisplatin were increased by 125%, 85% and 70%, respectively [13]. This shows that *C. cyminum* has a biopotentiation effect on drugs used in cancer treatments. Combining the anti-cancer drug sorafenib with thymoquinone and piperine (STP) enhanced the cytotoxic effect of the drug. The IC_{50} value of the drug was reduced to 1.54 µM when combined with thymoquinone and piperine relative to the IC_{50} of 10.83 µM when sorafenib was used alone in HepG2 hepatic cancer cell lines. In the breast cancer cell line MDA-MB-231, the combined effect of sorafenib, thymoquinone and piperine resulted in an almost five times reduction in the IC_{50} from 23.69 µM to 5.89 µM. The study also established that the expression of DNMT3B/HDAC3 genes decreased in an STP combination. The expression of the mutated DNMT3B gene is responsible for uncontrolled cell growth in a tumor, and it was decreased 5-fold in the STP combination, while the expression of the mutated HDAC 3 gene that prevents apoptosis in cancer cells was reduced by 3.8-fold, giving a clear understanding of the molecular mechanism involved in the biopotentiation

of the drugs [14]. Makhov et al., 2011, showed that piperine can increase the bioavailability of the anti-cancer drug docetaxel. Docetaxel is metabolized by the hepatic enzyme CYP3A4, and hence the inhibition of the enzyme can increase the bioavailability of the drug. The research has shown that the C_{max} of the drug increased to almost double from 6808 to 11,380 ng/mL in the presence of the bioenhancer piperine [15]. Similarly, tamoxifen, an anti-cancer drug, was metabolized by the CYP3A4 enzyme of the liver and intestine. A study performed by Kumar et al., 2015, showed that the C_{max} of tamoxifen was increased in the plasma of rats pretreated with curcumin or piperine. Both bioenhancers curcumin and piperine had a dose-dependent effect. Curcumin at a dosage of 10 mg/kg increased the C_{max} of tamoxifen from 73 ng/mL to 113 ng/mL, whereas 10 mg/kg of piperine increased it to 119 ng/mL [16]. Etoposide, a widely used anti-cancer drug, has the limitation of oral bioavailability of only 50%. However, when it was combined with an analog of piperidine PA1, the C_{max} increased by 76% [17]. Li and Choi showed that quercetin produced a major alteration in the pharmacokinetics of etoposide. The study showed that 15 mg/kg of quercetin could increase the C_{max} of etoposide from 484 µg/mL to 673 µg/mL [18]. In vivo experiments in rats demonstrated a dose-dependent response in the C_{max} with respect to quercetin. A concentration as low as 0.6 mg/kg of quercetin resulted in the elevation of the C_{max} of doxorubicin from 20 µg /mL to 27 µg /mL [19]. The in vivo experiments with rats also showed that the C_{max} of the anti-cancer drug paclitaxel doubled when given in combination with 20 mg/kg of quercetin [20]. Paclitaxel also showed a better retention and the area under curve (AUC) increased by almost 50% in rats that were pretreated with 10 mg/kg of naringin. Naringin is a known inhibitor of biliary P-gp and CYP3A1 [21]. The C_{max} of paclitaxel increased by 91% in the presence of 10 mg/kg of the potent bioenhancer genistein [22]. In an interesting study, the effect of the bioenhancers quercetin, kaempferol, genistein and daidzein were evaluated for their reversal of multidrug resistance (MDR) in the anti-cancer drug paclitaxel. It was found that, in a dose-dependent manner, kaempferol exhibited the most potent reversal of MDR in the human cervical carcinoma cells KB-V1. The IC_{50} for paclitaxel reduced to almost half in the presence of 30 µM of kaempferol. The effect was correlative to the fact that kaempferol markedly reduced the expression of P-gp in KB-V1 cells, as shown by immunoblotting [23]. Drug resistance for 5-FU, adriamycin, tamoxifen, paclitaxel and docetaxel for the gastric cell lines AGS-cyr61 overexpressing extracellular matrix-associated protein could be reversed by using quercetin, as shown in a study performed by Hyun et al., 2018 [24].

In recent times, several innovative drug delivery systems have been designed to appropriate the targeted delivery of drugs. These systems, such as liposomes, metallic nanoparticles, dendrimers, carbon nanotubes, etc., have been analyzed in vitro for the management of deadly diseases such as cancer. The main advantage of these drug carrier systems is their small size and excellent physicochemical properties, which result in the better pharmacokinetic properties of the drug compared to conventional drug delivery systems [25,26]. Gade et al., 2021, showed that a nanoemulsion prepared using MTX showed enhanced cytotoxicity when bioenhancers like piperine or quercetin were used. The half-life of the MTX–piperine nanoformulation increased to 6.1 h, while that of the MTX–quercetin nanoformulation increased to 8.2 h compared to the half-life of 3.6 h of the MTX nanoparticles. The enhanced cytotoxicity was also corroborated by the increased mean residence time of 8.2 h and 11.4 h in the MTX–piperine combination and MTX–quercetin combination, respectively, relative to 4.8 h in the MTX nanoparticles. These results establish the biopotentiation of MTX in the presence of piperine and quercetin [27]. The inhibitory activity of paclitaxel increased 5-fold in inhibiting the growth of MCF-7 breast cancer cells when treated with 1 µg/mL of glycyrrhizin [28]. Collectively, these reports empirically established that bioenhancers such as piperine, quercetin, thymoquinone, *C. cyminum*, naringin and genistein can play an important role in biopotentiating the effects of anti-cancer drugs; other bioenhancers are not addressed in this review because they have not been used as much in the biopotentaition of anti-cancer and anti-microbial agents.

2.2. Anti-Microbial Agents

There are several phytoconstituents that can act as bioenhancers in alleviating the potential of anti-microbial agents. The administration of bioenhancers can reduce the side effects and drug resistance problems, specifically in deadly infectious diseases such as tuberculosis. The following sections discuss the effect and impact of bioenhancers of varied classes on some of the most commonly used classes of anti-microbial agents, as shown in Figure 3.

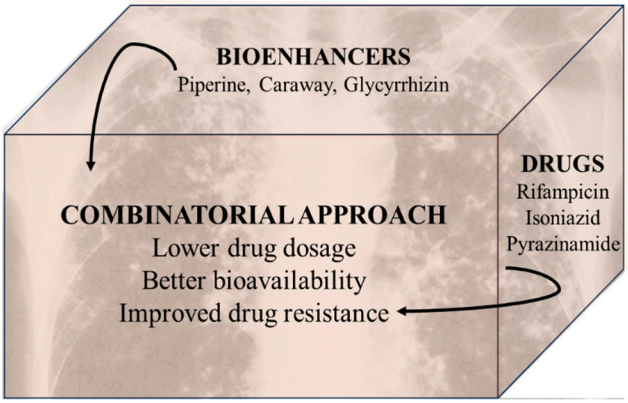

Figure 3. Combinatorial effect of bioenhancers and anti-tuberculosis agents.

2.2.1. Anti-Tubercular Agents

The FDC (fixed-dose combination) of rifampicin (R), isoniazid (I) and pyrazinamide (P) is the mainstay treatment for tuberculosis. However, it is marred by varied bioavailability in individuals. A study performed by Khajuria et al., 2014, showed that the addition of a natural bioenhancer, *Carum carvi* (*C. carvi*), led to increased levels of FDC drugs in the plasma. The addition of 100 mg *C. carvi* to the diet resulted in an increased C_{max} for the FDC drugs, where the C_{max} for rifampicin increased by 1.38-fold, while, for isoniazid, it increased by 0.98-fold and, for pyrazinamide, it increased by 6.2-fold. The pharmacokinetics data obtained in the study clearly indicate that *C. carvi* can potentially play the role of a bioenhancer [29].

Piperine is a known bioenhancer of drugs for the treatment of tuberculosis. It was shown that the addition of piperine could reduce the dosage of rifampicin from 450 mg to 200 mg. Piperine increases intestinal permeability by inhibiting the efflux pump, thereby elevating the absorption of the drug. In the case of tuberculosis, piperine is also known as an immunomodulator, and hence works in more than one mechanism [30]. Another study carried out on a group of 72 patients showed that the addition of piperine with a reduced dosage of rifampicin (200 mg) resulted in a faster sputum conversion rate and a statistically significant difference in the physiological parameters of the liver and kidney. The sputum conversion rate reduced from 1.947 and 1.912 in the usual care and intervention care to 0, respectively, at the end of the continuous phase [31]. A direct in vitro study on the *M. tuberculosis* H37Rv strain showed that the minimum inhibitory concentration (MIC) of rifampicin decreased by 66-fold when used with 200 µg/mL of a synthetic analog of Vitamin C (C11). The analog C11 was found to be non-toxic on the tested HepG2 cell line, while it demonstrated potent cytotoxicity against the bacterial strain H37Rv. C11 induced the production of reactive oxygen species inside of the macrophages and the bacterial strain, thereby attacking the microbe using more than one mechanism [32]. Glycyrrhizin at a concentration of 1 µg/mL could increase the activity of rifampicin by 14-fold [33]. The reduction in the drug dosage was the major beneficial aspect of using a bioenhancer as concluded by these studies.

2.2.2. Miscellaneous Agents

Enhanced pharmacokinetics with a lower drug dosage is the ideal situation to treat infectious diseases. Comprehensive research for effective drugs has been ongoing toward the treatment of deadly infections such as HIV. Nevirapine is a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase, which is used in combination with other anti-retroviral agents for the treatment of HIV-1 infection. According to a study performed by Kasibhatta and Naidu, 200 mg of Nevirapine when administered with 20 mg of piperine showed enhanced bioavailability. The C_{max} of Nevirapine in the plasma was found to increase by 120% [34]. Atazanavir, a protease inhibitor used as an anti-retroviral drug in HIV treatment, was found to have a better bioavailability in the presence of 30mg/kg of piperine and ginger oleoresin [35]. Declatasvir is an anti-viral drug used in the treatment of hepatitis C infection. It has a low bioavailability; however, in the presence of 10 mg/kg of curcumin, it was found to have an increased area under the curve of 8823 ng.h/mL relative to 7883 ng·h/mL [36]. Piperine at a concentration of 20 mg/kg was also found to increase the bioavailability of anti-microbial drugs such as ampicillin and norfloxacin. The study showed that, in an animal model, the C_{max} of 150 mg/kg of ampicillin increased from 44 to 251 µg/mL in the presence of piperine, whereas the C_{max} of 150 mg/kg of norfloxacin increased from 11 to 16 µg/mL [37]. Piperine was also found to increase the bioavailability of ciprofloxacin [38]. The administration of 10 mg/kg of piperine doubled the C_{max} of amoxicillin in rats. The same study also showed that the C_{max} of cefotaxime increased from 20 µg/mL to 31 µg/mL in the presence of 10 mg/kg of piperine. The bioavailability of gatifloxacin, an anti-bacterial used to treat eye infections, was enhanced in the presence of piperine, with a 1.3-fold increase in the C_{max} from 1.74 to 2.14 µg/mL [39].

Niaziridin, a nitrile glycoside extracted from moringa plant leaves, is known to biopotentiate the activity of several anti-microbial agents. Commonly used antibiotics such as rifampicin and nalidixic acid showed 38-fold and 50-fold increments in activity against *E. coli*. A minuscule amount of niaziridin, at 0.05 µg/mL, increased the activity of rifampicin against *B. subtilis* by about 20-fold [20]. Glycyrrhizin, another important biomolecule obtained from the plant *G. glabra*, was found to have a drastic effect in biopotentiating several anti-microbial drugs such as rifampicin, ampicillin, tetracycline and nalidixic acid to varying degrees [28]. Lysergol is a phytochemical obtained from the morning glory plant and it has been shown to possess a biopotentiating effect for several anti-microbial drugs, such as rifampicin, tetracycline and ampicillin. The study showed that 10 µg/mL of lysergol was enough to increase the bioavailability of rifampicin by 6–12 times [40]. In another study by Patil et al., 2011, it was shown that berberine, an anti-microbial phytoconstituent, increased the bioavailability in the presence of lysergol. As shown in vivo, lysergol at a dosage of 20 mg/kg body weight increased the C_{max} of berberine from 119 ng/mL to 191 ng/mL [41].

Several of these studies indicate the beneficial impacts of bioenhancers in potentiating the effects of drugs in the treatment of infectious diseases (Figure 4). Thus, it becomes imperative to divulge the mechanism of these bioenhancers.

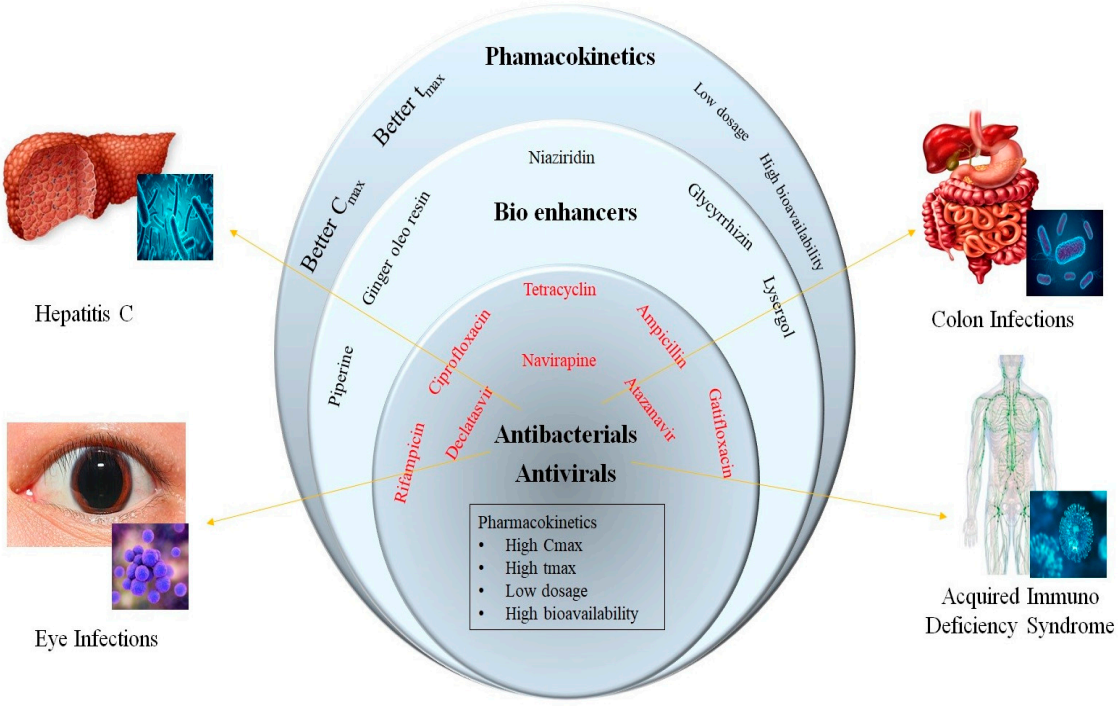

Figure 4. Effect of bioenhancers on the pharmacokinetics of anti-microbial agents involved in the treatment of various infections/diseases.

3. Mechanism of Action of Bioenhancers

There are several mechanisms that have been proposed by which bioenhancers exert their impact in biopotentiating the effect of various drugs. The section below discusses the major mechanism related to the action of bioenhancers.

3.1. Bypassing the Metabolism by Liver Enzymes

In an ideal scenario, a therapeutic drug must be able to penetrate the membrane and sustain in the circulation, bypassing the first-pass liver metabolism and rapid clearance by the kidneys. Challenges related to drug absorption are being addressed by the advancement of novel drug delivery systems. However, the first-pass metabolism can be overcome by inhibiting cytochrome P450 (CYP) family enzymes such as CYP3A4, CYP1A1, CYP1B2 and CYP2E1 present in the liver, gut, lungs and various other locations [42]. Among these, the CYP3A family is the most abundant subfamily in the liver and has different isoforms. CYP3A4 is one of the isoforms of the cytochrome P450 enzymes and is mostly found in the liver and small intestine. Many oral medications are metabolized by this enzyme, thereby reducing their bioavailability. CYP3A4 can be inhibited irreversibly by metabolites that can bind the enzyme and inactivate it. There are some known drugs that can inhibit CYP3A4, as well as herbs or fruits such as black pepper, grapefruit, etc. [43]. Figure 5 shows a diagrammatic representation of the effect of piperine in the drug metabolism in the liver involving the CYP3A4 enzyme. Cui et al., 2019, reported that approximately 50% of the enzyme activity was lost within 20 min with 80 µM of piperine. The kinetic studies showed that the mechanism-based inhibition was dependent on the concentration, time of incubation and NADPH (reduced nicotinamide adenine dinucleotide phosphate). Interestingly, the study also indicated that piperine contains a methylenedioxyphenyl ring (MDP), which is metabolized by CYP and is responsible for the inhibition of CYP3A4. The metabolite products of MDP, namely, carbene and quinine, could be the cause of irreversible enzyme inhibition [44].

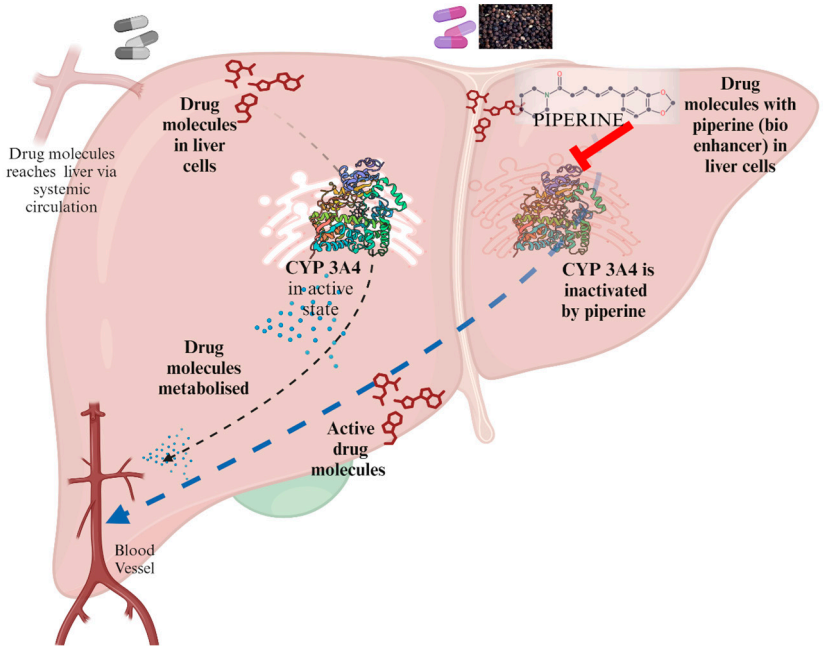

Figure 5. Drug molecules delivered into the liver via the portal vein are metabolized in the cells through the active CYP3A4 enzyme. The enzyme is located on the endoplasmic reticulum of the liver cells. The metabolic product of the drug then enters the systemic circulation, which is unavailable in its therapeutic form. Piperine inhibits the CYP3A4 enzyme by binding at the active site, rendering the enzyme inactive. The drug molecules can bypass the metabolism and enter the systemic circulation in its therapeutic form.

Furanocoumarins, present in grapefruit, are also metabolized by CYP3A4 to produce reactive intermediates that can covalently bind to the active site of CYP3A4, thereby resulting in the irreversible inactivation of the enzyme [43]. The furanocoumarin bergapten can inhibit CYP3A4 by up to 67%, as reported in a study conducted by Ho and Saville. The other components present in grapefruit, such as quercetin and naringenin, inhibited 55% and 39% of the CYP3A4 enzyme activity, respectively. Thus, there is a collective inhibitory effect of grapefruit juice in the inhibition of the CYP3A4 enzyme [45]. In a study performed by Kondza et al., 2021, it was shown that flavonols can interact and bind with the heme group of CYP3A4, resulting in its inhibition. The kinetic studies show that there is a possible covalent binding of the inhibitor at the active site of the enzyme [46]. Quercetin showed a concentration-dependent inhibition of CYP3A4, with a 50% inhibition at 1.97 μM. The study indicated that the concurrent administration of quercetin can possibly increase the bioavailability of doxorubicin by inhibiting the CYP3A4 enzyme [19]. In another study by Mohos et al., 2020, a relatively weaker inhibition of 30% to 45% of CYP3A4 was observed at a 30 μM concentration of quercetin [47]. A study conducted by Ostlund and coworkers also corroborated the inhibitory protection of quercetin towards CYP3A4, albeit the inhibition was less than 50%. The Ki of 15.4 μM for quercetin was reported for the competitive inhibition of recombinant human CYP3A4 [48]. These studies indicate that flavanols should be consumed with care if a patient is undergoing treatment for severe diseases such as diabetes, cancer, etc.

Interestingly, in the docking studies performed by Zhou et al., 2015, it was shown that major components of ginger interacted with the active site of the CYP3A4 enzyme via π–π stacking, and the pharmacokinetic studies showed that the $[I]/[K_i]$ value ranged from 0.0002 to 19.6, indicating drug–enzyme interaction. The study concluded that ginger components can result in variations in the drug response due to their ability to regulate the activity of CYP enzymes [49]. Similar conclusions can be drawn from another study performed by Mian et al., 2013. In this study, the pungent components in ginger, specifically

8- and 10-gingerol, inhibited the CYP3A4 enzyme, with an IC_{50} value of 8.7 µmol/L, and also decreased the expression by about 60% in an in vitro HepG2 cell line [50].

Thymoquinone, found in black seed, is also a potent inhibitor of liver enzymes. As shown by Albassam et al., 2018, 100 µM of thymoquinone could inhibit 79% of the CYP3A4 enzyme activity in human liver microsomes [51]. The above reports clearly indicate the irreversible inhibition of the CYP3A4 enzyme by the herbal bioenhancers, either directly or by their metabolites. Most of the bioenhancers discussed above could inhibit the enzyme activity by 50% or more by binding at the active site.

3.2. Inhibiting the P-gp Efflux Pump

P-glycoprotein (P-gp), also known as multidrug resistance protein 1 (MDR1), is expressed in the liver and intestine. P-gp is a member of the ATP-binding cassette transporter family. P-gp is comprised of two nucleotide-binding domains and two transmembrane domains that open inside of the lipid bilayer. Due to its unique structure, P-gp can bind to many substrates, resulting in the efflux of almost all chemotherapy drugs [52–54]. This results in the extrusion of many drugs, thereby limiting their absorption and hence their bioavailability [55]. The inhibition of P-gp can result in increased drug bioavailability. A plethora of molecules have been identified and developed as P-gp inhibitors. However, natural compounds have attracted more interest because of their inert and non-toxic properties. As shown in Figure 6, a natural bioenhancer is shown as an inhibitor of P-gp. Piperine is known to be a potent inhibitor of P-gp, as shown by Bhardawaj et al., 2002. The research tested the transport of two drugs, digoxin and cyclosporin A. It was found that the apical-to-basal P_{app} for digoxin in Caco2 monolayer cells increased from 1.37 in the control to 7 in the presence of 250 µM of piperine, while the P_{app} from basal to apical decreased from 11.6 in the control to 7.5 in the presence of 250 µM of piperine. A similar trend was reported for cyclosporin A as well, indicating an inhibition of P-gp by piperine. The IC_{50} value for piperine was reported to be 15.5 and 74.1 µM for digoxin and cyclosporin A, respectively. The study also indicated that a soup containing 1 g of piperine would most likely be a high enough concentration to inhibit the P-gp in the small intestine [2]. The strong inhibitory activity of piperine is because it can bind the nucleotide-binding domain of P-gp, which is crucial for ATP-coupled drug efflux through the P-gp pump. This competitive binding of piperine is also observed by piperine analogs [56]. The P-gp inhibitory effect of piperine makes it a bioenhancer for many chemotherapeutic drugs. In a study performed by Syed et al., 2017, two piperine analogs, Pip1 and Pip2, were tested for their ability to act as bioenhancers for chemotherapeutic drugs. The mechanism of P-gp inhibition was studied for the two analogs. In an in vitro test in P-gp-overexpressing KB (cervical) and SW480 (colon) cancer cells, it was found that both analogs Pip1 and Pip2 could reverse the resistance towards vincristine, colchicine or paclitaxel. The molecular docking data from the study suggested that both Pip1 and Pip2 could bind the P-gp protein, with G scores of −7.99 and −8.16, respectively. The low potential energies of 2.16 $kJmol^{-1}$ and 2.14 $kJmol^{-1}$ for the Pip1-P-gp and Pip2-P-gp complexes, respectively, indicated that the complexes formed were stable. In the in vitro studies carried out in the KB ChR 8-5-resistant cell line, the IC_{50} for vincristine decreased from 36 nM to 3 nM in the presence of Pip1 and to 11.47 in the presence of Pip2. A similar pattern was shown for the IC_{50} of colchicine and paclitaxel [57]. The IC_{50} of paclitaxel in the MDCK cell lines was 46 µg/mL, which was significantly higher than 11.2 µg/mL in the MDCK-MDR1 cell lines, thereby indicating that there is a correlation between the drug resistance and P-gp expression. Moreover, it was found that the addition of 10 µg/mL of piperine enhanced the accumulation of the drug in MDCK-MDR1 cells by 1.85-fold. Molecular docking studies revealed that piperine and paclitaxel shared many binding residues on P-gp, with piperine exhibiting a higher affinity. Piperine at a concentration of 20 µg/mL was found to decrease the P-gp protein content by 28% by downregulating the *mdr1* gene expression as evaluated by Western blot and RT-qPCR studies [58]. It has been shown that piperine binds at the nucleotide-binding domain, which is crucial for ATP-coupled efflux through P-gp. The binding occurs between

the consensus sequence of the Walker A/P loop and Walker C loop (linker peptide). The piperine analogs Pip1 and Pip2 have also been shown to bind at the ATP-binding site in P-gp [56].

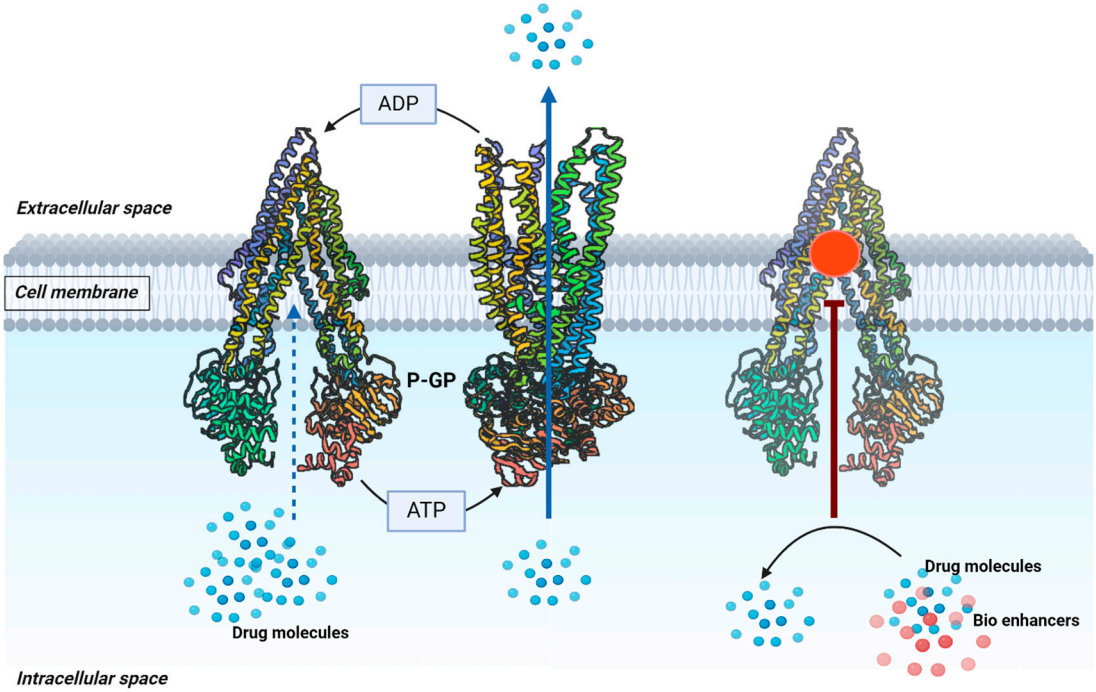

Figure 6. Drug molecules (blue dots) are exported out of the cell through the P-gp protein. The ATP-dependent P-gp protein conformation changes from open inside (intracellular space) to open outside (extracellular space), resulting in the efflux of drug molecules. A bioenhancer (red dots) such as piperine binds to the nucleotide-binding domain of P-gp and inhibits the protein pump, resulting in the retention of drug molecules inside of the cell.

3.3. Miscellaneous Mechanisms

Uridine 5′-diphospho-glucuronosyltransferase (UDP-GT) is a phase II metabolism enzyme catalyzing the glucuronidation of xenobiotics in the gut, resulting in their elimination. Piperine was shown to lower the UDP–glucuronic acid content and also inhibited the transferase activity [59]. Zhang et al., 2021, showed that quercetin exerted a strong competitive binding with the recombinant isoforms of the UDP-GT enzyme. The IC_{50} of quercetin was found to be about 7 μM in inhibiting the enzyme activity, thereby implicating its role in the bioavailability of drugs that are metabolized by UDP-GT in the second phase of the metabolism [60].

A study conducted by Jia et al., 2016, demonstrated that resveratrol was found to reduce the renal clearance of methotrexate by 37%. The results were corroborated by examining the uptake of methotrexate in kidney slices, where it was found that the uptake of the drug was significantly reduced in the presence of resveratrol [61]. The oral bioavailability of a drug largely depends on its ability to penetrate the gastrointestinal epithelial membrane. Some of the other postulated effects of bioenhancers are by increasing the blood supply in the gastrointestinal (GI) tract and by regulating the permeability of the epithelial cells of the GI tract. Bajad et al., 2001, reported that piperine could reduce the gastric emptying time for solids at a dosage of 1 mg/kg in rats [62]. The mutation frequency of DNA due to a drug such as ciprofloxacin was reduced in the presence of piperine. The mutation prevention concentration of ciprofloxacin in the presence of piperine was found to be 4 mg/L, which is 16 times higher than the minimum inhibitory concentration of the drug [63]. Such mechanisms help the bioenhancers to potentiate the effect of therapeutic drugs and can potentially change the dosage of a drug while reducing the drug resistance.

4. Natural Bioenhancers in Novel Drug Delivery Formulations

Natural bioenhancers also have the limitations of poor solubility and bioavailability. As discussed earlier in the text, these limitations can be overcome by formulating the active ingredient/bioenhancers in novel drug delivery systems. This section will focus exclusively on the role of bioenhancers in novel formulations, excluding the discussions of other formulation types of bioenhancers. There are several bioenhancers that have been formulated in liposomes, nanoparticles, transferosomes and microspheres. It has been shown by Gade et al., 2021, that nanoparticles composed of paclitaxel, quercetin and piperine increased the bioavailability of paclitaxel by at least three times [27]. Ray et al., 2020, also prepared guar gum-coated enteric nanoparticles consisting of amphotericin B and piperine, and reported that this formulation could increase the anti-bacterial activity of amphotericin B by 96% against the parasite *Leishmania* [64]. The encapsulation of isradipine with the bioenhancer rutin in solid lipid nanoparticles enhanced the oral bioavailability of isradipine by 3.2–4.7-fold [65]. A calcium channel blocker, nisoldipine, when formulated with piperine in PGLA-coated nanoparticles, increased the bioavailability of the drug [66]. In another study by Pingale et al., 2014, some parameters of drugs used in the treatment of tuberculosis were studied. It was reported that microspheres prepared by using isoniazid and rifampicin had increased the bioadhesion in the presence of the bioenhancer by 20%. Bioadhesion is a vital parameter for the enhanced absorption of drugs, thereby increasing their bioavailability. The in vitro release kinetics also doubled from 45% to 90% in the presence of bioenhancers. The bioenhancer used was hydro-alcoholic extracts of *Carum carvi* and *Ocimum sanctum* [67]. Similarly, there are other studies that prove that the addition of a bioenhancer can result in an incremental increase in the bioavailability of various drugs formulated in nanoformulations [3]. Cadila Pharma's commercial formulation of the anti-tubercular drug Risorine combination of rifampicin with piperine resulted in a 60% increase in the bioavailability, and piperine also resulted in the dosage reduction in rifampicin from 450 mg to 200 mg, thereby decreasing the drug cost, required dosage and toxicity [3]. Curcumin is incorporated in several nanoformulations and it has been reported to increase the pharmacological activity of drug molecules. Curcumin itself exhibits hepatoprotective, anti-fibrotic and anti-neoplastic effects through the activation and inhibition of various signal transduction pathways, demonstrating good clinical efficacy and minimal adverse reactions [68]. Recent research shows that curcumin nanoformulations exhibit enhanced pharmacological action (anti-microbial) when combined with other agents like antibiotics, and hence the combinatorial approach can be beneficial for a successful treatment strategy [69]. Research reports on the incorporation of bioenhancers into nanoformulation approaches/novel drug delivery systems or their combination with drugs for enhanced delivery are currently quite limited.

5. Clinical Studies to Assess the Safety and Effectiveness of Bioenhancers

The safety and efficacy of natural bioenhancers and the need to improve the therapeutic effect of drugs have led to the study of the role of bioenhancer agents in clinical trials. A recent interventional non-randomized study evaluated the administration of piperine to biopotentiate the effect of curcumin in treating patients with advanced cervical cancer. The study involved 30 patients divided into six groups receiving different concentrations of curcumin (1–6 g) with piperine. The study is expected to provide results by the year 2025 (NCT06080841) [70]. Another interventional study with nine patients in phase I trial employed piperine to enhance the effect of curcumin in early prostate cancer (NCT02598726) [71]. In a recent ongoing, randomized, double-blinded interventional phase II clinical trial, 30 patients were enrolled, where curcumin was tested for its therapeutic effect on myeloproliferative neoplasms. Piperine was administered as a bioenhancer along with curcumin for a period of 12 months. The study is expected to be completed by 2027, where primary outcomes will be measured with respect to changes in inflammatory cytokine levels in the blood, correlating it with the improvement in symptoms. The secondary

outcomes of the study measure the demethylation pattern in DNA, changes in blood counts and safety/toxicity of curcumin in patients (NCT06063486) [72].

Chemotherapy causes various side effects such as oral mucositis in patients with blood malignancies. In a clinical study completed in 2012, 20 patients undergoing chemotherapy were enrolled; however, no results have been published (NCT01732393) [73]. In an ongoing study conducted in Cairo, quercetin nanoparticles coated in PGLA are being tested for their efficacy in treating squamous cell tongue carcinoma (NCT05456022) [74]. In a double-blinded randomized trial with 32 patients, quercetin is also being evaluated for its preventive effect on prostate cancer (NCT01912820) [75]. In a triple-blinded randomized interventional study, 60 patients were enrolled to study the effect of quercetin and genistein on prostate cancer. The primary outcome of the study will include monitoring the increase in prostate-specific antigen (PSA), while the secondary outcome will assess prostate cancer incidence and the safety/toxicity of quercetin and genistein (NCT01538316) [76]. In an interesting study, quercetin was used as a bioenhancer with the chemotherapeutic drug dasatinib in the reversal of drug resistance in triple-negative breast cancer. It was demonstrated in the preclinical studies that a combination of dasatinib and quercetin with chemotherapy could effectively eliminate chemotherapy-induced senescent fibroblasts, decrease the proliferation rate of disseminated tumor cells and ultimately lead to a significant reduction in metastasis and recurrence, thereby enhancing the efficacy of chemotherapy. The complete results of the study are awaited (NCT06355037) [77].

In a phase I/II intervention clinical trial with patients undergoing treatment for colorectal cancer, genistein, when combined with FOLFOX-Bevacizumab, resulted in lowering the adverse effects of chemotherapy. Patients were given a 60mg daily dose of genistein for 7 days every 2 weeks, followed by a chemotherapeutic drug. The encouraging results of the 61% best overall response rate (BOR) and 11.5 months of progression-free survival (pfs) warrant a larger verification trial (NCT01985763) [78]. In another clinical trial, the effect of genistein was evaluated in children with leukemia and solid tumors being treated with the chemotherapeutic drug decitabine. The results of the study have not been published (NCT02499861) [79]. The biopotentiation of interleukin-2 with genistein was studied on 15 patients suffering from metastatic melanoma; however, no results have been posted (NCT00276835) [80]. The preventive effect of genistein in 24 patients with squamous cell carcinoma of the head and neck receiving chemoradiation therapy was studied. The study, however, did not publish any results (NCT02075112) [81]. In treating pancreatic cancer, combining genistein with gemcitabine and erlotinib can possibly increase the bioavailability of the drugs. A clinical trial conducted on 20 patients remained inconclusive (NCT00376948) [82]. As reported by Messing et al., genistein can slow down the tumor progression in patients with bladder cancer undergoing surgery (NCT00118040) [83].

Tuberculosis intervention requires long-term therapy, which leads to various side effects, specifically gastrointestinal disturbances. A randomized intervention clinical study used *Zingiber officinale*, *Carum carvi* L. and *Mentha spicata* L. to alleviate the effects of antituberculosis drugs on the gastric system. The study plan, with about 200 patients, was to divide them into four groups, one group receiving the placebo (100 mg/day), another group receiving zingiber powder (500 mg × 2/day), another receiving carum powder (1 g × 2/day) and another receiving mentha oil (1.5 mL × 2/day). The treatment was planned to be given for 3 months; however, the details of the outcome are still awaited (NCT06157034) [84].

Though there are several clinical trials that have been conducted to assess the biopotentiation of various drugs using natural bioenhancers, there are few that have been completed. There has only been one marketed formulation, Risorine, comprised of 10 mg of piperine, 300 mg of isoniazid and 200 mg of rifampicin, for the treatment of tuberculosis [3]. There is a need for more trials to arrive at a conclusive inclusion of natural bioenhancers in therapeutic drugs.

6. Patent Review

The importance of bioenhancers in elevating the availability of various drugs is evident from the patent applications filed/granted in different studies. Table 1 below lists the patents where herbal/natural bioenhancers are used for increasing the bioavailability of antibiotics, nutritional compounds, anti-tubercular agents and treatment modalities.

Table 1. Patents filed for bioenhancers.

S. No.	Bioenhancer	Bioenhancement of Drugs/Nutrients	Patent Number
1	Piperine	Essential nutrients and supplements	US 5536506 [85]
2	Gingerin Piperine Gingerin + Piperine	Several drugs, especially anti-cancer and anti-infective agents/nutrients	EP 1465646A1 [86]
3	Niaziridin	Antibiotics	US 6858588 B2 [87]
4	Glycyrrhizin	Antibiotics	US 6979471B1 [28]
5	Piperine	Nutritional compounds	US 5972382 [88]
6	Piperine and its derivatives	Essential nutrients and supplements	US 6849645 [89]
7	Cow urine distillate	Antibiotics	US 6410059B1 [90]
8	*C. Carvi*	-	US 0020347A1 [91]
9	Piperine	Anti-TB drug	EP 0650728B1 [92]
10	Cumin	-	US 007514105B2 [13]
11	Essential oil	Curcumin	US 9861677B2 [93]
12	Lysergol (*Rivea corymbosa*)	Antibiotics	US 20070060604A1 [40]
13	*Stevia rebaudiana*	-	US 20100112101A1 [94]

From the reported patents shown in Table 1, it is observed that several patents focus on the bioenhancement properties of piperine, which can increase the absorption of various drugs, essential nutrients and supplements, making them more effective. Piperine's ability to inhibit drug efflux pumps in cancer cells has been patented for use in combination therapies, enhancing the efficacy of certain chemotherapeutic agents. Despite numerous reports from researchers on the bioenhancement properties of phytoconstituents, there is a scarcity of filed patents related to their pharmaceutical application.

7. Conclusions and Future Prospects

Drug discovery, design and development are challenging aspects for deadly diseases, such as cancer, and certain infections, such as HIV and tuberculosis. The treatments can last long and are a financial burden for the patients. Hence, the drug design should minimize the cost and side effects. Co-administration of a bioenhancer along with a drug can be a potential strategy to overcome the limitations in drug design. The present review highlighted selective bioenhancers and their role in improving the therapeutics of drugs primarily in diseases such as cancer and infections such as tuberculosis and HIV. The effect of bioenhancers is mediated by inhibiting the enzymes involved in the elimination of drugs (xenobiotics) from the body. Two such mechanisms are active in the liver and intestine, the cytochrome P450 enzyme family and the p-glycoprotein efflux pump, and they are inhibited by bioenhancers, thereby facilitating the retention of the drug in the target area and increasing its bioavailability.

There are considerable challenges that patients and healthcare systems encounter that not only require scientific innovation but also a compassionate approach to patient care. The mechanisms by which bioenhancers exert their effect are well documented in most of the literature reviewed, offering insights that can optimize drug effectiveness by precisely targeting specific sites by the novel formulation approach. This provides an intriguing perspective on the potential of bioenhancers in improving the therapeutic efficacy of drugs. The potential of these bioenhancers can further be exploited by using nanoformulations for better absorption. The clinical studies and patents filed suggest an ever-growing interest in the strategy of using bioenhancers to augment the bioavailability of therapeutics. While

discussing the benefits of increased bioavailability, the importance of thorough investigations into its toxicity profile cannot be emphasized enough. Achieving a balance between enhanced therapeutic effects and the risk of potential overdosing requires careful attention and diligence. This warrants a strict rational drug design approach to avoid drug overdosing due to extended retention in body fluids. Hence, there is a requirement to understand the toxicity of bioenhancer compounds for the safe administration of therapeutic drugs, and this part is missing in most of the existing literature. Overall, the approach of including a bioenhancer in a drug regime could bring about a paradigm shift in the treatment of the most difficult diseases, including cancer and infections. However, the regulation of the drug design using a synergistic approach for bioenhancers with the drug must be very strict.

Author Contributions: Conceptualization, D.U.M., G.K.N. and S.A.K.; methodology, D.U.M. and G.K.N.; software, D.U.M. and G.K.N. validation, S.A.K. and A.A.; formal analysis, S.A.K.; resources, D.U.M., G.K.N. and M.J.A.; data curation, D.U.M., G.K.N. and M.J.A.; writing—original draft preparation, D.U.M., G.K.N., M.J.A. and S.A.K.; writing—review and editing, S.A.K., M.J.A. and A.A.; visualization, D.U.M., G.K.N. and M.J.A.; supervision, S.A.K., M.J.A. and A.A.; project administration, D.U.M., S.A.K., M.J.A. and A.A.; funding acquisition, D.U.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received financial support from the Ministry of Higher Education, Research & Innovation (MoHERI), Oman, under grant no. BFP/RGP/HSS/22/220.

Acknowledgments: The authors would like to thank the College of Pharmacy, National University of Science and Technology, Oman, for providing necessary research facilities.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AGS-cyr 61	Gastric adenocarcinoma cysteine-rich angiogenic inducer 61
ATP	Adenosine triphosphate
AUC	Area under the curve
B. subtilis	*Bacillus subtilis*
C max	Maximum serum concentration
C. carvi	*Carum carvi*
C. cyminum	*Cuminum cyminum*
Caco2	Cancer coli-2 cells
Carum carvi L.	*Carum carvi* Linnaeus
COVID	Coronavirus disease 2019
CYP	Cytochrome
DNA	Deoxy ribonucleic acid
DNMT3B	DNA methyltransferase 3B
E. coli	*Escherichia coli*
EP	European patent
FDC	Fixed-dose combination
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FU	5-Fluorouracil
G. glabra	*Glycyrrhiza glabra*
GI	Gastrointestinal tract
H37Rv	Mycobacterium tuberculosis strain H37 rough virulent
HDAC3	Histone deacetylase 3
HepG2	Hepatoblastoma cell line
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
I	Isoniazid
IC50	Half-maximal inhibitory concentration
KB	KERATIN-forming tumor cell line HeLa.
KB-V1	Multidrug-resistant human KB carcinoma cells

MCF	Michigan Cancer Foundation-7
MDA-MB-231	M.D. Anderson metastasis breast cancer
MDCK	Madin–Darby canine kidney
MDCK-MDR1	Madin–Darby canine kidney cells transfected with either the multidrug resistance gene-1
MDP	Methylenedioxyphenyl ring
MDR	Multidrug resistance
Mentha spicata L.	*Mentha spicata* Linnaeus
MIC	Minimum inhibitory concentration
MTX	Methotrexate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NCT	National clinical trial
P	Pyrazinamide
P450	Cytochrome P450
Papp	Apparent permeability coefficient
PGLA	Poly lactic-co-glycolic acid
P-gp	P-glycoprotein
R	Rifampicin
RT-qPCR	Quantitative reverse-transcription polymerase chain reaction
STP	Sorafenib with thymoquinone and piperine
SW480	Cells from the large intestine of a Dukes C colorectal cancer patient
t max	Maximum time
UDP-GT	Uridine 5′-diphospho-glucuronosyltransferase
US	United States
WHO	World Health Organization
µM	Micromolar

References

1. Ahamad, J. A Comprehensive Review on Natural Bioenhancers. *Int. Res. J. Pharm.* **2019**, *10*, 1–5. [CrossRef]
2. Bhardwaj, R.K.; Glaeser, H.; Becquemont, L.; Klotz, U.; Gupta, S.K.; Fromm, M.F. Piperine, a Major Constituent of Black Pepper, Inhibits Human P-Glycoprotein and CYP3A4. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 645–650. [CrossRef]
3. Thorat, S.S.; Gujar, K.N.; Karale, C.K. Bioenhancers from Mother Nature: An Overview. *Future J. Pharm. Sci.* **2023**, *9*, 20. [CrossRef]
4. Jhanwar, B.; Gupta, S. Biopotentiation Using Herbs: Novel Technique for PoorBioavailable Drugs. *Int. J. PharmTech Res.* **2014**, *6*, 443–454.
5. Drabu, S.; Khatri, S.; Babu, S.; Lohani, P. Use of Herbal Bioenhancers to Increase the Bioavailability of Drugs. *Res. J. Pharm. Biol. Chem. Sci.* **2011**, *2*, 107–119.
6. Randhawa, G.; Kullar, J. Rajkumar Bioenhancers from Mother Nature and Their Applicability in Modern Medicine. *Int. J. Appl. Basic Med. Res.* **2011**, *1*, 5. [CrossRef]
7. Global Cancer Burden Growing, Amidst Mounting Need for Services. World Health Organization. 2024. Available online: https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services (accessed on 7 July 2024).
8. Fleck, A. *TB Is the World's Second Deadliest Infectious Disease*; Statista: London, UK, 2023.
9. Nishat, A.; Thaiseen, S.; Rajesh, B.; Sama, V. A Strategy to Enhance Bioavailability of Drug Candidates: Natural Bioenhancers. *SunText Rev. Pharm. Sci.* **2021**, *1*, 10–14. [CrossRef]
10. Breedveld, P.; Beijnen, J.H.; Schellens, J.H.M. Use of P-Glycoprotein and BCRP Inhibitors to Improve Oral Bioavailability and CNS Penetration of Anticancer Drugs. *Trends Pharmacol. Sci.* **2006**, *27*, 17–24. [CrossRef]
11. Kang, M.J.; Cho, J.Y.; Shim, B.H.; Kim, D.K.; Lee, J. Bioavailability Enhancing Activities of Natural Compounds from Medicinal Plants. *J. Med. Plant Res.* **2009**, *3*, 1204–1211.
12. Tripathi, A.K.; Ray, A.K.; Mishra, S.K. Molecular and Pharmacological Aspects of Piperine as a Potential Molecule for Disease Prevention and Management: Evidence from Clinical Trials. *Beni-Suef Univ. J. Basic Appl. Sci.* **2022**, *11*, 16. [CrossRef]
13. Qazi, G.N.; Bedi, K.L.; Johri, R.K.; Tikoo, M.K.; Tikoo, A.K.; Sharma, S.C.; Abdullah, S.T.; Suri, O.P.; Gupta, B.D.; Suri, K.A.; et al. Bioavailability/Bioefficacy Enhancing Activity of Cuminum cyminum and Extracts and Fractions Thereof. U.S. Patent US007514105B2, 7 April 2009.
14. El-Shehawy, A.A.; Elmetwalli, A.; El-Far, A.H.; Mosallam SA, E.R.; Salama, A.F.; Babalghith, A.O.; Mahmoud, M.A.; Mohany, H.; Gaber, M.; El-Sewedy, T. Thymoquinone, Piperine, and Sorafenib Combinations Attenuate Liver and Breast Cancers Progression: Epigenetic and Molecular Docking Approaches. *BMC Complement. Med. Ther.* **2023**, *23*, 69. [CrossRef] [PubMed]
15. Makhov, P.; Golovine, K.; Canter, D.; Kutikov, A.; Simhan, J.; Corlew, M.M.; Uzzo, R.G.; Kolenko, V.M. Co-Administration of Piperine and Docetaxel Results in Improved Anti-Tumor Efficacy via Inhibition of CYP3A4 Activity. *Prostate* **2011**, *72*, 661–667. [CrossRef] [PubMed]

16. Kumar, V.; Mittal, V. Pawan Jalwal Role of Herbal Bioenhancers (Piperine and Curcumin) on the Oral Bioavailability of Tamoxifen Using Experimental Rats. *J. Pharmacogn. Phytochem.* **2015**, *4*, 133–136.
17. Najar, I.A.; Sharma, S.C.; Singh, G.D.; Koul, S.; Gupta, P.N.; Javed, S.; Johri, R.K. Involvement of P-Glycoprotein and CYP 3A4 in the Enhancement of Etoposide Bioavailability by a Piperine Analogue. *Chem.-Biol. Interact.* **2011**, *190*, 84–90. [CrossRef] [PubMed]
18. Li, X.; Choi, J.-S. Effects of Quercetin on the Pharmacokinetics of Etoposide after Oral or Intravenous Administration of Etoposide in Rats. *PubMed* **2009**, *29*, 1411–1415.
19. Choi, J.-S.; Piao, Y.-J.; Kang, K.W. Effects of Quercetin on the Bioavailability of Doxorubicin in Rats: Role of CYP3A4 and P-Gp Inhibition by Quercetin. *Arch. Pharmacal Res.* **2011**, *34*, 607–613. [CrossRef]
20. Dudhatra, G.B.; Mody, S.K.; Awale, M.M.; Patel, H.B.; Modi, C.M.; Kumar, A.; Kamani, D.R.; Chauhan, B.N. A Comprehensive Review on Pharmacotherapeutics of Herbal Bioenhancers. *Sci. World J.* **2012**, *2012*, 637953. [CrossRef]
21. Lim, S.-C.; Choi, J.-S. Effects of Naringin on the Pharmacokinetics of Intravenous Paclitaxel in Rats. *Biopharm. Drug Dispos.* **2006**, *27*, 443–447. [CrossRef]
22. Li, X.; Yun, J.; Choi, J. Effects of Morin on the Pharmacokinetics of Etoposide in Rats. *Biopharm. Drug Dispos.* **2007**, *28*, 151–156. [CrossRef]
23. Limtrakul, P.; Khantamat, O.; Pintha, K. Inhibition of P-Glycoprotein Function and Expression by Kaempferol and Quercetin. *J. Chemother.* **2005**, *17*, 86–95. [CrossRef]
24. Hyun, H.; Moon, J.; Cho, S. Quercetin Suppresses CYR61-Mediated Multidrug Resistance in Human Gastric Adenocarcinoma AGS Cells. *Molecules* **2018**, *23*, 209. [CrossRef] [PubMed]
25. Berg, S.L.; Tolcher, A.; O'Shaughnessy, J.A.; Denicoff, A.M.; Noone, M.; Ognibene, F.P.; Cowan, K.H.; Balis, F.M. Effect of R-Verapamil on the Pharmacokinetics of Paclitaxel in Women with Breast Cancer. *J. Clin. Oncol.* **1995**, *13*, 2039–2042. [CrossRef] [PubMed]
26. Unnikrishnan Meenakshi, D.; Narde, G.K.; Ahuja, A.; Al Balushi, K.; Francis, A.P.; Khan, S.A. Therapeutic Applications of Nanoformulated Resveratrol and Quercetin Phytochemicals in Colorectal Cancer—An Updated Review. *Pharmaceutics* **2024**, *16*, 761. [CrossRef] [PubMed]
27. Gade, J.; Jain, B.; Rawat, R.; Prashant Sharma, P.; Gupta, P. An Effective Nanoparticles for Drug Delivery System. *Mater. Today Proc.* **2021**, *51*, A1–A7. [CrossRef]
28. Khanuja SP, S.; Kumar, S.; Arya, J.S.; Shasany, A.K.; Singh, M.; Awasthi, S.; Gupta, S.C.; Darokar, M.P.; Rahman, L.U. Composition Comprising Pharmaceutical/Nutraceutical Agent and a Bioenhancer Obtained from Glycyrrhizaglabra. U.S. Patent US006979471B1, 27 December 2005.
29. Khajuria, V.; Tandon, V.; Arora, E.; Choudhary, N.; Gillani, Z. Effect of Carum Carvi, a Herbal Bioenhancer on Pharmacokinetics of Antitubercular Drugs: A Study in Healthy Human Volunteers. *Perspect. Clin. Res.* **2014**, *5*, 80. [CrossRef]
30. Prasad, R.; Singh, A.; Gupta, N.; Tarke, C. Role of Bioenhancers in Tuberculosis. *Int. J. Health Sci. Res.* **2016**, *6*, 307–313.
31. Nageswari, A.D.; Rajanandh, M.G.; Uday, M.K.R.A.; Nasreen, R.J.; Pujitha, R.R.; Prathiksha, G. Effect of Rifampin with Bio-Enhancer in the Treatment of Newly Diagnosed Sputum Positive Pulmonary Tuberculosis Patients: A Double-Center Study. *J. Clin. Tuberc. Other Mycobact. Dis.* **2018**, *12*, 73–77. [CrossRef]
32. Bokolia, N.P.; Bag, K.; Sarkar, B.; Jhawar, R.; Chatterji, D.; Jayaraman, N.; Ghosh, A. A Novel Vitamin c Analog Acts as a Potent Bio-Enhancer to Augment the Activities of Anti-Tuberculosis Drugs against *Mycobacterium Tuberculosis*. *bioRxiv* **2023**. [CrossRef]
33. Khanuja, S.P.S.; Kumar, S.; Arya, J.S.; Shasany, A.K.; Singh, M.; Awasthi, S. Composition Comprising Pharmaceutical/Nutraceutical Agent and a Bioenhancer Obtained from Glycyrrhizaglabra. U.S. Patent US20060057234A1, 16 March 2006.
34. Kasibhatta, R.; Naidu, M.U.R. Influence of Piperine on the Pharmacokinetics of Nevirapine under Fasting Conditions. *Drugs R D* **2007**, *8*, 383–391. [CrossRef]
35. Prakash, S.; Kherde, P.; Rangari, V. Bioenhancement Effect of Piperine and Ginger Oleo Resin on the Bioavailability of Atazanvir. *Int. J. Pharm. Pharm. Sci./Int. J. Pharm. Pharm. Sci.* **2015**, *7*, 241–245.
36. Magotra, A.; Kotwal, P.; Bhatt, S.; Dogra, A.; Singh, G.; Nandi, U. Impact of Concomitantly Administered Curcumin on Pharmacokinetics of Daclatasvir in Mice under the Frame of Herb-Drug Interaction. *Indian J. Pharm. Educ.* **2018**, *52*, s11–s15. [CrossRef]
37. Janakiraman, K.; Manavalan, R. Studies on Effect of Piperine on Oral Bioavailability of Ampicillin and Norfloxacin. *Afr. J. Tradit. Complement. Altern. Med.* **2008**, *5*, 257–262. [CrossRef] [PubMed]
38. Balakrishna, B.S.; Yogesh, P.V. Influence of Co-Administration of Piperine on Pharmacokinetic Profile of Ciprofloxacin. *Indian Drugs* **2002**, *39*, 166–168.
39. Patel, S.; Devada, S.; Patel, H.; Patel, N.; Bhavsar, S.; Thaker, A. Influence of Co-Administration of Piperine on Pharmacokinetic Profile of Gatifloxacin in Layer Birds. *Glob. Vet.* **2011**, *7*, 427–432.
40. Khanuja, S.; Arya, J.; Srivastava, S.; Shasany, A.; Kumar, T.S.; Darokar, M.; Kumar, S. Antibioticpharmaceutical Composition with Lysergol as Bioenhancerand Method of Treatment. U.S. Patent US20070060604A1, 15 March 2007.
41. Patil, S.; Dash, R.P.; Anandjiwala, S.; Nivsarkar, M. Simultaneous Quantification of Berberine and Lysergol by HPLC-UV: Evidence that Lysergol Enhances the Oral Bioavailability of Berberine in Rats. *Biomed. Chromatogr.* **2011**, *26*, 1170–1175. [CrossRef]
42. Tatiraju, D.V.; Bagade, V.B.; Karambelkar, P.J.; Jadhav, V.M.; Kadam, V. Natural Bioenhancers: An Overview. *J. Pharmacogn. Phytochem.* **2013**, *2*, 55–60.

43. Bailey, D.G.; Dresser, G.; Arnold, J.M.O. Grapefruit–Medication Interactions: Forbidden Fruit or Avoidable Consequences? *Can. Med. Assoc.* **2013**, *185*, 309–316. [CrossRef]
44. Cui, T.; Wang, Q.; Tian, X.; Zhang, K.; Peng, Y.; Zheng, J. Piperine Is a Mechanism-Based Inactivator of CYP3A. *Drug Metab. Dispos.* **2019**, *48*, 123–134. [CrossRef]
45. Ho, P.-C.; Saville, D.J. Sompon Wanwimolruk Inhibition of Human CYP3A4 Activity by Grapefruit Flavonoids, Furanocoumarins and Related Compounds. *PubMed* **2001**, *4*, 217–227.
46. Kondža, M.; Bojić, M.; Tomić, I.; Maleš, Ž.; Rezić, V.; Ćavar, I. Characterization of the CYP3A4 Enzyme Inhibition Potential of Selected Flavonoids. *Molecules* **2021**, *26*, 3018. [CrossRef]
47. Mohos, V.; Fliszár-Nyúl, E.; Ungvári, O.; Kuffa, K.; Needs, P.W.; Kroon, P.A.; Telbisz, Á.; Özvegy-Laczka, C.; Poór, M. Inhibitory Effects of Quercetin and Its Main Methyl, Sulfate, and Glucuronic Acid Conjugates on Cytochrome P450 Enzymes, and on OATP, BCRP and MRP2 Transporters. *Nutrients* **2020**, *12*, 2306. [CrossRef] [PubMed]
48. Östlund, J.; Zlabek, V.; Zamaratskaia, G. In Vitro Inhibition of Human CYP2E1 and CYP3A by Quercetin and Myricetin in Hepatic Microsomes Is Not Gender Dependent. *Toxicology* **2017**, *381*, 10–18. [CrossRef] [PubMed]
49. Zhou, S.-F.; Qiu, J.; Zhou, Z.-W.; He, Z.; Zhang, X.; Zhu, S. Estimation of the Binding Modes with Important Human Cytochrome P450 Enzymes, Drug Interaction Potential, Pharmacokinetics, and Hepatotoxicity of Ginger Components Using Molecular Docking, Computational, and Pharmacokinetic Modeling Studies. *Drug Des. Dev. Ther.* **2015**, *9*, 841–866. [CrossRef] [PubMed]
50. Li, M.; Chen, P.; Yue, Q.; Li, J.; Chu, R.; Zhang, W.; Wang, H. Pungent Ginger Components Modulates Human Cytochrome P450 Enzymes in Vitro. *Acta Pharmacol. Sin.* **2013**, *34*, 1237–1242. [CrossRef]
51. Albassam, A.A.; Ahad, A.; Alsultan, A.; Al-Jenoobi, F.I. Inhibition of Cytochrome P450 Enzymes by Thymoquinone in Human Liver Microsomes. *Saudi Pharm. J.* **2018**, *26*, 673–677. [CrossRef]
52. Alam, A.; Kowal, J.; Broude, E.; Roninson, I.; Locher, K.P. Structural Insight into Substrate and Inhibitor Discrimination by Human P-Glycoprotein. *Science* **2019**, *363*, 753–756. [CrossRef]
53. Wang, H.; Liang, Y.; Yin, Y.; Zhang, J.; Su, W.; White, A.M.; Jiang, B.; Xu, J.; Zhang, Y.; Stewart, S.; et al. Carbon Nano-Onion-Mediated Dual Targeting of P-Selectin and P-Glycoprotein to Overcome Cancer Drug Resistance. *Nat. Commun.* **2021**, *12*, 312. [CrossRef]
54. Kim, Y.; Chen, J. Molecular Structure of Human P-Glycoprotein in the ATP-Bound, Outward-Facing Conformation. *Science* **2018**, *359*, 915–919. [CrossRef]
55. Crowe, A.; Tan, A.M. Oral and Inhaled Corticosteroids: Differences in P-Glycoprotein (ABCB1) Mediated Efflux. *Toxicol. Appl. Pharmacol.* **2012**, *260*, 294–302. [CrossRef]
56. Rather, R.A.; Bhagat, M. Cancer Chemoprevention and Piperine: Molecular Mechanisms and Therapeutic Opportunities. *Front. Cell Dev. Biol.* **2018**, *6*, 10. [CrossRef]
57. Syed, S.B.; Arya, H.; Fu, I.-H.; Yeh, T.-K.; Periyasamy, L.; Hsieh, H.-P.; Coumar, M.S. Targeting P-Glycoprotein: Investigation of Piperine Analogs for Overcoming Drug Resistance in Cancer. *Sci. Rep.* **2017**, *7*, 7972. [CrossRef] [PubMed]
58. Xu, W.; Xiao, Y.; Zheng, L.; Xu, M.; Jiang, X.; Wang, L. Enhancing Paclitaxel Efficacy with Piperine-Paclitaxel Albumin Nanoparticles in Multidrug-Resistant Triple-Negative Breast Cancer by Inhibiting P-Glycoprotein. *Pharmaceutics* **2023**, *15*, 2703. [CrossRef] [PubMed]
59. Singh, S.; Tripathi, J.; Rai, N. An Appraisal of the Bioavailability Enhancers in Ayurveda in the Light of Recent Pharmacological Advances. *AYU (Int. Q. J. Res. Ayurveda)* **2016**, *37*, 3. [CrossRef] [PubMed]
60. Zhang, R.; Wei, Y.; Yang, T.; Huang, X.; Zhou, J.; Yang, C.; Zhou, J.; Liu, Y.; Shi, S. Inhibitory Effects of Quercetin and Its Major Metabolite Quercetin-3-O-β-D-Glucoside on Human UDP-Glucuronosyltransferase 1A Isoforms by Liquid Chromatography-Tandem Mass Spectrometry. *Exp. Ther. Med.* **2021**, *22*, 842. [CrossRef] [PubMed]
61. Jia, Y.; Liu, Z.; Wang, C.; Meng, Q.; Huo, X.; Liu, Q.; Sun, H.; Sun, P.; Yang, X.; Ma, X. P-Gp, MRP2 and OAT1/OAT3 Mediate the Drug-Drug Interaction between Resveratrol and Methotrexate. *Toxicol. Appl. Pharmacol.* **2016**, *306*, 27–35. [CrossRef] [PubMed]
62. Bajad, S.; Bedi, K.L.; Singla, A.K.; Johri, R.K. Piperine Inhibits Gastric Emptying and Gastrointestinal Transit in Rats and Mice. *Planta Medica* **2001**, *67*, 176–179. [CrossRef] [PubMed]
63. Kumar, A.; Khan, I.A.; Koul, S.; Koul, J.L.; Taneja, S.C.; Ali, I.; Ali, F.; Sharma, S.; Mirza, Z.M.; Kumar, M.; et al. Novel Structural Analogues of Piperine as Inhibitors of the NorA Efflux Pump of Staphylococcus Aureus. *J. Antimicrob. Chemother.* **2008**, *61*, 1270–1276. [CrossRef]
64. Ray, L.; Karthik, R.; Srivastava, V.; Singh, S.P.; Pant, A.B.; Goyal, N.; Gupta, K.C. Efficient Antileishmanial Activity of Amphotericin B and Piperine Entrapped in Enteric Coated Guar Gum Nanoparticles. *Drug Deliv. Transl. Res.* **2020**, *11*, 118–130. [CrossRef]
65. Kumar, V.; Chaudhary, H.; Kamboj, A. Development and Evaluation of Isradipine via Rutin-Loaded Coated Solid–Lipid Nanoparticles. *Interv. Med. Appl. Sci.* **2018**, *10*, 236–246. [CrossRef]
66. Rathee, P.; Kamboj, A.; Sidhu, S. Enhanced Oral Bioavailability of Nisoldipine-Piperine-Loaded Poly-Lactic-Co-Glycolic Acid Nanoparticles. *Nanotechnol. Rev.* **2017**, *6*, 517–526. [CrossRef]
67. Pingale, P.L.; Pandharinath, R.R.; Shrotriya, P.G. Study of Herbal Bioenhancers on Various Characteristics of Isoniazid and Rifampicin Microspheres. *Int. J. Infect. Dis.* **2014**, *21*, 235. [CrossRef]
68. Gao, T.H.; Liao, W.; Lin, L.T.; Zhu, Z.P.; Lu, M.G.; Fu, C.M.; Xie, T. Curcumae rhizoma and its major constituents against hepatobiliary disease: Pharmacotherapeutic properties and potential clinical applications. *Phytomedicine* **2022**, *102*, 154090. [CrossRef] [PubMed]

69. Bertoncini-Silva, C.; Vlad, A.; Ricciarelli, R.; Giacomo Fassini, P.; Suen, V.M.M.; Zingg, J.-M. Enhancing the Bioavailability and Bioactivity of Curcumin for Disease Prevention and Treatment. *Antioxidants* **2024**, *13*, 331. [CrossRef] [PubMed]
70. Curcumin Supplementation in Cervical Cancer. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT06080841 (accessed on 24 June 2024).
71. Curcumin and Piperine in Reducing Inflammation for Ureteral Stent-Induced Symptoms in Patients with Cancer. Available online: https://clinicaltrials.gov/study/NCT02598726 (accessed on 24 June 2024).
72. Curcumin to Improve Inflammation and Symptoms in Patients with Clonal Cytopenia of Undetermined Significance, Low Risk Myelodysplastic Syndrome, and Myeloproliferative Neoplasms. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT06063486 (accessed on 24 June 2024).
73. Effect of Quercetin in Prevention and Treatment of Oral Mucositis. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT01732393 (accessed on 24 June 2024).
74. Therapeutic Efficacy of Quercetin Versus Its Encapsulated Nanoparticle on Tongue Squamous Cell Carcinoma Cell Line. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT05456022 (accessed on 24 June 2024).
75. Effect of Quercetin on Green Tea Polyphenol Uptake in Prostate Tissue from Patients with Prostate Cancer Undergoing Surgery. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT01912820 (accessed on 24 June 2024).
76. Prostate Cancer Prevention Trial with Quercetin and Genistein (QUERGEN). Available online: https://classic.clinicaltrials.gov/ct2/show/NCT01538316 (accessed on 24 June 2024).
77. Dasatinib Combined with Quercetin to Reverse Chemo Resistance in Triple Negative Breast Cancer. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT06355037 (accessed on 24 June 2024).
78. Genistein in Treatment of Metastatic Colorectal Cancer. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT01985763 (accessed on 24 June 2024).
79. Phase I/II a Study of Decitabine in Combination with Genistein in Pediatric Relapsed or Refractory Malignancies. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT02499861 (accessed on 24 June 2024).
80. Genistein and Interleukin-2 in Treating Patients with Metastatic Melanoma or Kidney Cancer. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT00276835 (accessed on 24 June 2024).
81. Soy Isoflavone in Combination with Radiation Therapy and Cisplatin in SCC of the Head and Neck. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT02075112 (accessed on 24 June 2024).
82. Genistein, Gemcitabine, and Erlotinib in Treating Patients with Locally Advanced or Metastatic Pancreatic Cancer. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT00376948 (accessed on 24 June 2024).
83. Phase II Study of Isoflavone G-2535 (Genistein) in Patients with Bladder Cancer. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT00118040 (accessed on 24 June 2024).
84. Prokinetic Effect of Selected Nutraceuticals. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT06157034 (accessed on 24 June 2024).
85. Majeed, M.; Badmaev, V.; Rajendran, R. Use of Piperine to Increase the Bioavailability of Nutritional Compounds. U.S. Patent USOO5536506A, 28 April 1996.
86. Qazi, G.N.; Tikoo, L.; Gupta, A.K.; Ganju, K.; Gupta, D.K.; Jaggi, B.S. Bioavailability Enhancing Activity of Zingiber Officinale Linn and Its Extracts/Fractions Thereof. European Patent EP1465646A1, 12 December 2002.
87. Khanuja, S.P.S.; Arya, J.S.; Tiruppadiripuliyur, R.S.K.; Saikia, D.; Kaur, H.; Singh, M.; Gupta, S.C.; Shasany, A.K.; Darokar, M.P.; Srivastava, S.K.; et al. Nitrile Glycoside Useful as a Bioenhancer of Drugs and Nutrients, Process of Its Isolation from Moringa Oleifera. U.S. Patent US 6858588 B2, 31 March 2003.
88. Majeed, M.; Badmaev, V.; Rajendran, R. Use of Piperine as a Bioavailability Enhancer. U.S. Patent US5972382, 26 October 1999.
89. Majeed, M.; Badmaev, V.; Rajendran, R.; Prakash, S.; Natarajan, S. Method of Increased Boavailability of Nutrients and Pharmaceutical Preparations with Tetrahydropperine and its Analogues and Dervatives. U.S. Patent US6849645, 1 February 2005.
90. Khanuja, S.P.S.; Kumar, S.; Shasany, A.K.; Arya, J.S.; Darokar, M.P.; Singh, M.; Sinha, P.; Awasthi, S.; Gupta, S.C.; Gupta, V.K.; et al. Pharmaceutical Composition Containing Cow Urine Distillate and an Antibiotic. U.S. Patent US 6410059B1, 25 June 2002.
91. Qazi, G.N.; Bedi, K.; Johri, R.; Tikoo, M.; Tikoo, A.; Sharma, S.; Abdullah, T.; Suri, O.; Gupta, B.; Suri, K.; et al. Bioavailability Enhancing Activity of Carum Carvi Extracts and Fractions Thereof. U.S. Patent US20070020347A1, 25 January 2007.
92. Kapil, R.S.; Zutshi, U.; Bedi, K.L.; Singh, G.; Johri, R.K.; Dhar, S.K.; Kaul, J.L.; Sharma, S.C.; Pahwa, G.S.; Kapoor, N.; et al. Pharmaceutical Compositions Containing Piperine and an Antituberculosis or Antileprosydrug. European Patent EP 0650728B1, 3 May 1995.
93. Benny, A. Composition to Enhance the Bioavailability of Curcumin. United. U.S. Patent US 9861677B2, 9 January 2018.
94. Gokaraju, G.R.; Gokaraju, R.R.; D'Souza, C.; Frank, E. Bio-Availability/Bio-Efficacy Enhancing Activity of Stevia Rebaudiana and Extracts and Fractions and Compounds Thereof. U.S. Patent US20100112101A1, 6 May 2010.