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BIOAVAILABILITY OF PHYTOCHEMICALS FROM NATURAL PRODUCTS, FOOD AND FOOD SUPPLEMENTS: IMPROVEMENT OF THE PHARMACOKINETICS BY DRUG DELIVERY SYSTEMS

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ABSTRACT

The there is a global strong interest to improve the therapeutic value of drugs through the improvement of bioavailability of many active compounds. The co-administration of active pharmaceutical agents from natural products with improved absorption activities has gained great interest in oral drug delivery. Many phytochemicals from medicinal plants have shown their capacity to improve the bioavailability of co-administered drugs by inhibiting efflux pumps or oxidative metabolism, and influencing the intestinal brush border membrane. Some of these known natural bioactive compounds include quercitine, genistein, glycyrrhizin, nitrile glycosides, sinomenine, piperine, naringin, and many others under study. The status of human nutrition also constitutes an important determinant of the quality of life, morbidity, and mortality. With an increase in nutraceutical potential of foods and food supplement, supported by the claims of health benefits, researchers have strong advocacy awareness and accountability for regulatory compliance of the therapeutic and toxicologic effect of phytochemicals, nutritional supplements and foods. To address the challenges of safety and quality of phytochemicals, an understanding of bioavailability of these products becomes evident. For a better increasing understanding of nutraceuticals, it is important to have an increased understanding of nutrition and therefore physicians, allied health practitioners, patients, and public health policy makers have more sensitization to better understand the basis for efficacy and safety of nutritional supplements and foods. Novel delivery systems that modulate the pharmacokinetics of existing drugs, such as nanoparticles, cyclodextrins, niosomes, liposomes, could be exploited to enhance the delivery of bioactive compounds and enhanced bioavailability at target sites. This review gives an insight into bioavailability in natural products phytochemicals as one of the factors that can enhance significantly the pharmacokinetic profile of a drug. This paper discusses the improvement of drug bioavailability exhibited by natural compounds from plants, some of the delivery approaches that have already made an impact by either delivering a drug to target tissue or increasing its bioavailability by many fold changes.

KEYWORDS: Bioavailability, phytochemicals, pharmacokinetics, natural products, food, toxicology, microbiome, dietary intake, metabolism.

1. INTRODUCTION

The increased advances and interest in drug design technologies has significantly influenced research in druggable new chemical entities (NCE). These NCE are faced with major challenges of low bioavailability with the enteral oral route of administration that is influenced

by poor permeation across the gastrointestinal epithelia.[1] Drugs may have low membrane permeability, due to low lipophilicity and zwitterionic character at physiological pH[2], or may have poor water solubility or efflux by P-glycoprotein (P-gp).[3] There has been great advancement and interest of oral drug absorption and bioavailability within the pharmaceutical industries. Many approaches have been exploited and described to enhance the intestinal absorption through the use of absorption enhancers, prodrugs and permeability, and enhancement of dosage forms (liposomes and emulsions).[1] The application of P-gp inhibitors most recently in improving enteral drug delivery has also gained research interest.[4] A global increase has been reported in the medicinal plants and food supplement market with a sale of around US$104 billion.[1,5] This rapid expanding market has led to an increased concern dealing with public health associated issues.

One of the main public health issues include the lack of information on the bioavailability of phytochemicals from natural products, micronutrients from various sources. There has been an advancement in research on the bioavailability of phytochemicals and micronutrients in most Pharma industries.[5,6] There is an increased need in the understanding of the principles of pharmacokinetics as they relate to the impact of phytochemicals, dietary supplement and food matrices on micronutrient bioavailability, while investigating the distinction between nutrient content and biological relevance.[2,3] Examination of phytochemical like polyphenols and their role in the management of diverse pathologies such as cancer and cardiovascular diseases is emerging and supports our better understanding that the health effects of polyphenols clearly depends on their bioavailability and subsequent utilization in target tissues.[4] The understanding of bioavailability is also critical in micronutrients contained in nutritional supplements as compared with those in the food matrix.[5]

1.1. Phytochemicals compounds produced by plants

Phytochemicals are compounds that are produced by plants and some are well known to act as defense to protect cells from damage that could lead to some pathological disorders.[6,7] They are found in food (fruits, vegetables, grains, beans), and other plants. The US Food, Drug, and Cosmetic Act[6] defines a dietary supplement as a product "intended to supplement the diet" that contains one or more of the following: a vitamin, mineral, herb or botanical, or amino acid, or "a dietary substance for use by man to supplement the diet through an increase in the total dietary intake" or a "concentrate, metabolite, constituent, extract, or combination of the above.".[2,4,7] In contrast, food has a far more broad definition[8] as "any substance used for food or drink for man or other animals, chewing gum, and articles used for components of any other such article." Food supplements are specific mineral substitute to food and derived from natural products, with lesser regulatory compliance than drug.[9] Nutrients and foods are dietary components that are consumed orally and require supralingual mixing, mastication, and esophageal transit into the stomach and small intestine for further digestion or absorption.[9,10] The two broad classes of dietary components (supplements and foods) contain micronutrients that play an important role in human health and disease state management not on the therapeutic basis.[4,11]

1.2. Microelements

Micronutrients are only required in traceable doses but can produce multiple biological activities with the potential to regulate normal growth, development, and cellular and physiological functions.[11,12] They vitamins, phytochemicals, and minerals such as iron, cobalt, chromium, copper, iodine, selenium, zinc, and chromium.[7,12] Bioavailability of micronutrients is conventionally defined as the fraction of a given dose of unchanged nutrient that reaches the systemic circulation.[3] For dietary supplements, herbal products, and other nutrients in which the route of administration is mainly oral, the bioavailability concerns the quantity or fraction of the ingested dose that is absorbed.[2,7,13] Bioavailability for dietary supplements can be grouped into two parts, as the proportion of the administered substance capable of being absorbed and that available for cellular uptake, use, or storage.[2,14]

1.3. Bioavailability concepts

In pharmacology, bioavailability is considered as the proportion of a drug or other substance which enters the systemic circulation when introduced into the body for therapeutic effect.[1] Bioavailability is therefore a subcategory of absorption, and is the fraction of an administered drug that reaches the systemic circulation. When a drug is administered by parenteral route of administration such as, intravenously, the bioavailability is 100% or absolute bioavailability.[2] Issues of poor oral bioavailability of drugs for many therapeutic disease areas have hindered progress in disease prevention. The state-of-the-art delivery systems that modulate the pharmacokinetics (PK) of existing drugs, such as nanoparticles, cyclodextrins, niosomes, liposomes and implants, are now very useful to enhance the delivery of drugs to target sites. The development of new approaches in prevention and treatment of diseases now exploits new delivery systems subject to regulatory approved for integration into study of newly investigated bioactive compounds.[3,4,15]

1.4. Pharmaceutics Effect

Pharmaceutics deals with the scientific and technical aspects of the design and manufacture of dosage forms. The understanding of the physical chemistry necessary for efficient design of dosage forms (Physical pharmaceutics), the understanding of relevant body systems and how drugs arrive there, following administration (biopharmaceutics).[3] The design and formulation of medicine (dosage form design), the

manufacture of these medicines on both a small (compounding) and large (pharmaceutical technology) scale are part of pharmaceutics. The avoidance and elimination of microorganisms in medicines (pharmaceutical microbiology).[4-6] The schematic diagram in Figure 1 illustrates the relationship between biopharmaceutics, pharmacokinetics and pharmacodynamics.

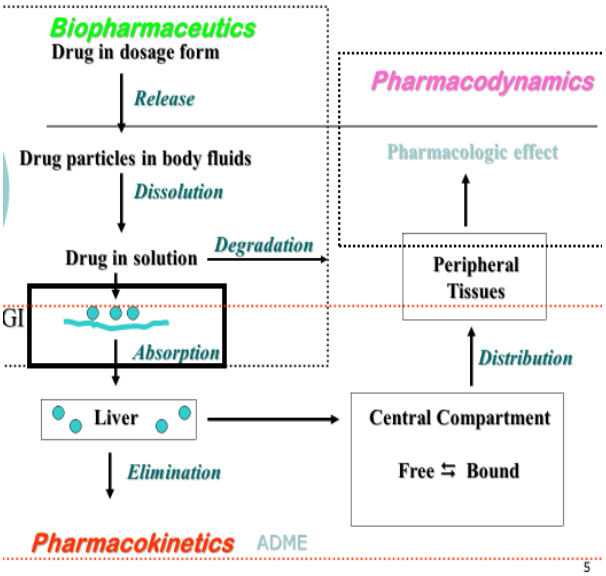

Figure 1 The relationship between biopharmaceutics, pharmacokinetics and pharmacodynamics.[8]

There is an interrelationship between absorption, distribution, metabolism and elimination that defines pharmacokinetics as shown in figure 2.

1.5. Pharmacokinetics (PK)

This is the study of how the body interacts with administered drugs for the entire duration of exposure. This is closely related to but distinctly different from pharmacodynamics, which examines the drug's effect on the body more closely.[2,3] Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, though, and out of the body, the time course of its absorption. Pharmacokinetics can vary from person to person and it is affected by age, gender, diet, environment, body weight and pregnancy, patient's pathophysiology, genetics and drug- drug or food-drug interactions.[4,5] The four main parameters generally examined by this field include absorption, distribution, metabolism, and excretion (ADME). What is pharmacodynamics with example?

1.6. Pharmacodynamics (PD)

The study of the biochemical and physiological effects of drugs and their mechanisms of action. Pharmacodynamic parameters relate the pharmacokinetic factors to the ability of an antimicrobial to kill or inhibit the growth of the infecting organism.[3] PD deals with biochemical, physiological, and molecular effects of drugs on the body and involves receptor binding (including receptor sensitivity), post receptor effects, and chemical interactions. Pharmacodynamic actions include: stimulating activity by directly inhibiting a receptor and its downstream effects. Depressing activity by direct receptor inhibition and its downstream effects. Antagonistic or blocking a receptor by binding to it, but not activating.[2,3] In a more simplistic manner PD is concern with the action of drug on the body.

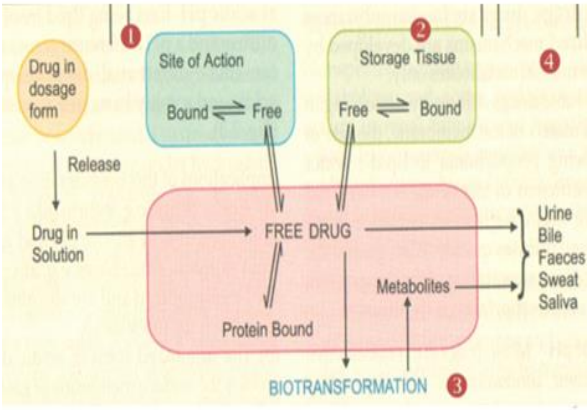

Figure 2. show the pharmacokinetics relationship of absorption, distribution, metabolism and elimination.[8]

Drugs given intravenously the total dose of the drug administered reaches systemic circulation, and the drug is said to be 100% bioavailable. The fraction of drug which reaches systemic circulation following administration by another route is known as the bioavailable dose.[14] The relative amount of dose of a particular drug that reaches the systemic circulation intact and the rate at which this occurs is known as the bioavailability. Bioavailability is the rate and extent of drug absorption.[6,7] Figure 3 illustrate systemic circulation and pathway of bioavailable drug.

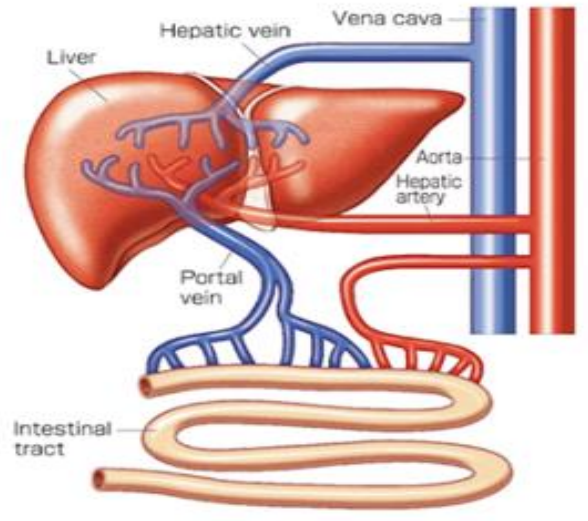

Figure 3: Illustration of systemic circulation and pathway of bioavailable drug.[3,8]

1.7. Host predispositions in bioavailability

Human host physiology and metabolism is very complex and diversified within subject population temporally and between subjects as a function of different variables: such as; Fed or fasted state of the individual, dietary load, source and food matrix, general health and state of gastrointestinal tract (rate of gastric emptying, motility status, time of day and life style factors, the state of acute or chronic illness of the individual such as hepatic insufficiency and impaired renal function, pregnancy.[2,9,15] For Chronic cases, the following are considered postoperative status as exemplified by active recovery from surgical intervention and wound healing stage, athletic status (example ongoing athletic training or weekend athlete), nutritive status (such as malnutrition or nutrient insufficiency), age extremes (such as in general, drugs are metabolized more slowly in fetal, neonatal and geriatric population.[16,17]

1.8. Food and Nutraceutical factors in PK bioavailability

The physicochemical dietary property has a significant effect on the host processing of micronutrients and also in the chemistry of digestion, absorption, and distribution. The presence and content of other nutrients such as; high levels of zinc decrease Fe and Cu absorption; vitamin C, a potent reducing agent improves nonheme Fe absorption; and vitamin D improves Ca, P, and Mg transport and absorption. Since carotenoids are fat soluble, the addition of small quantities of fat or oil will enhance bioavailability.[4,18] Interactions with other drugs/foods, for example, antacids, alcohol, and nicotine; inhibitory interaction effects can be nutritionally advantageous as in the case of dose-appropriate phytosterols that may be an adjunct for lowering the absorption of low-density lipoprotein cholesterol in patients with hyperlipidemia.[8,19] Interactions with other foods (such as grapefruit juice, apple juice, brassica vegetables) via enzymatic inhibition can decrease the rate of metabolism, like in the case of grapefruit juice inhibits CYP3A.

Physical properties of a drug like hydrophobicity, pKa, solubility, particle size, and binding cations represent significant variables, that can all influence bioavailability. The drug formulation and encapsulation, excipients used, manufacturing methods, immediate release, modified release, delayed release, extended release, and sustained release, and dosage all contribute to bioavailability enhancement.[20] Apart from vitamin C, smaller doses of nutrients do appear to increase the percentage of nutrient absorbed. However, a modification of dosage form, does not seem to affect significantly the location of maximum absorption along the gastrointestinal tract. Water-soluble nutrients, both vitamin C and mineral salts initially appear to be absorbed quite rapidly. Mineral salts, like zinc, a delay appears before a second phase of absorption can occur along the gut.[6,21] The lipophilic nutrient, carotene, appears to be more slowly absorbed, but this is said to reflect the time needed to produce an emulsified or protein-bound form compatible with transport into the serum, to facilitate bioavailability. The reduced bioavailability of carotene and vitamin E in soft gel form may also be related to competition with the vegetable oil-based vehicle, present in excess, for emulsification by chylomicrons integral to absorption.[7,22] This is in contrast to the normal expectation of the impact of oil-based delivery in the presence of an emulsifier.

Generally, it is considered that micronutrients that are intrinsic to food and those that are delivered through supplements have variations in bioavailability that are mediated via a complex system of processes and interactions. These collectively can be understood in terms of the Absorption, Distribution, Metabolism, and Excretion (ADME) model, which was developed in order to characterize the pharmacokinetics of drugs and xenobiotics in general. Unlike many drugs, micronutrients may not act efficiently in isolation but together with compounds in the food matrix may have synergistic effects.[4,13,23]

2.0. MICROBIOME EFFECT ON BIOAVAILABILITY

The gut microbes contribute to biosynthesis and bioavailability of vitamins and phytochemicals from natural products. However, the impact of this contribution, the role of microflora in the catabolism of polyphenols and the production of some active metabolites in healthy and unhealthy patients are still not well understood.[14,24] The complex architecture of the microbiome may affect bioavailability of xenobiotics. The molecular structure for example of bacterially synthesized vitamins is not always identical to the dietary forms of the vitamins. Many specialized epithelial transporters have been shown to participate in a specific manner in the absorption of vitamins derived from gut bacteria.[15,24] Many reports focus on the understanding of the mechanisms and regulation of transport of water-soluble vitamins at the cellular and molecular levels. In addition, the regulatory regions of the genes that encode a number of the involved transporters have been cloned and characterized in transgenic mice, thus providing more information on the transcriptional regulation of these events.[11,25] There is a better understanding of the mechanisms involved in intracellular cell trafficking and membrane targeting of the carrier proteins, and how clinically significant mutations may result in dysfunctional transport.

The identification of efficient and specialized carrier-mediated systems in the large intestine that are capable of absorbing a number of bacterially synthesized vitamins (thiamin, folate, biotin, riboflavin, pantothenic acid) increases the possibility that this source of vitamins may play a significant role in regulating the normal body homeostasis of these vitamins and, in turn, that of supplemental vitamins.[9,26] In terms of the microbiome and macronutrients, another interesting and still

unresolved dimension is the recycling of intestinal nitrogen and bacterial amino acids to the systemic metabolism. One additional set of bacteria-related variables influencing bioavailability is to do with the high interindividual variability in human subjects observed in some metabolic processes, in which the microflora is involved.[26]

2.1. Bioavailability and its impact on the microbiota

Early studies show that the gut microflora have a major contribution to the biosynthesis and bioavailability of vitamins and microelements. On the other hand, the impact of their contribution and their role in the catabolism of polyphenols and the production of some bioactive metabolites in healthy and unhealthy volunteers is not well understood.[14] The contributions of microbiomes in the bioavailability of xenobiotics has generated so much research interest in recent years and the molecular structure of a bacterially synthesized vitamin is not always identical to the dietary forms of the vitamins. In addition, many specialized epithelial transporters are known to participate specifically in the absorption of vitamins derived from gut bacteria.[15,24] There is a significant pool of finding that highlights the understanding of the mechanisms and regulation of transport of water-soluble vitamins at the cellular and molecular levels. Furthermore, the regulatory regions of the genes that encode a number of the involved transporters have been cloned and characterized in transgenic mice, which provide an insight into the transcriptional regulation of these events.[11,25] There is an understanding of the mechanisms involved in intracellular trafficking and membrane targeting of the carrier proteins and how clinically significant mutations may result in dysfunctional transport.

The identification of an efficient and specialized carrier mediated systems in the large intestine that are capable of absorbing a number of bacterially synthesized vitamins such as thiamin, folate, biotin, riboflavin, pantothenic acid confirms the possibility that this source of vitamins could play a major role in the regulation of the normal body homeostasis of these vitamins and, in turn, that of supplemental vitamins.[9,26] In terms of the microbiome and macronutrients, another interesting but still unresolved dimension is the recycling of intestinal nitrogen and bacterial amino acids to the systemic metabolism. One important aspect of the bacteria-related diversity depends on bioavailability which influences the high interindividual variation in human subjects observed in some metabolic processes, especially those in which the microflora is involved.[26]

2.2. Bioavailability of the Phytochemical polyphenols

Polyphenols (polyhydroxyphenols) are compounds, that the human physiology does not produce them. They are secondary metabolites of plants, macromolecules of molecular weights between 500 and 4000 Da, with at least 12 phenolic hydroxyl groups, 5–7 aromatic rings per 1000 Da, and significant binding affinity for proteins.[17,27] Large conjugated systems of pi electron configurations impart distinctive ultraviolet/visual absorption characteristics. *In vitro* studies have shown the activity of individual dietary polyphenols as potent free-radical scavengers, but, like so many observations in medical nutrition research, research findings need to be backup by *in vivo* studies with special consideration to appropriate dosing in relation with real-life intake patterns.[12] More than 8000 polyphenolic compounds have been identified in many plant families and various plant species.[8,28] All plant phenolic compounds are known to be derived from a common intermediate, phenylalanine, or a close precursor, shikimic acid. Polyphenols occur mostly in conjugated forms, with one or more sugar residues linked to the hydroxyl groups. Their association with other compounds, such as carboxylic and organic acids, amines, lipids and linkage with another phenol, is also common.[19]

Polyphenols have been well reviewed.[20,29] Showing great level of complexity and variability in the biochemistry and possible clinical relevance of these compounds. Polyphenols are categorized into different groups based on the number of phenol rings that they contain and on the basis of structural elements that bind these rings to one another.[6,30] The main classes include phenolic acids, flavonoids, stilbenes, and lignans. Bioavailability appears to differ greatly among the various polyphenols, and the most abundant polyphenols in the human diet are not necessarily those that have the best bioavailability profile.[31] Prasain et al. reviewed the risks and benefits of dietary phenolics (flavonoids, in this case) as compared with those delivered via supplements.[2, 32] Supplements containing flavonoids and isoflavonoids have been greatly criticized, due to adverse endocrine effects likely related to dose and bioavailability.[33] Major aspects that deserve more attention when estimating bioavailability include effects of innovative processing techniques, synergistic effects of mixed/whole diets, factors effecting micelle formation, co-constituents influencing influx and efflux via transporter systems, or altering phase I/II metabolism, as these have often been overlooked or excluded from consideration, in part due to the difficulties to include in their study in vivo or in vitro.[20]

Polyphenols are extensively modified, not only in the small intestine and colon but also in the liver, where most conjugation process takes place. Any single polyphenol may generate two or three metabolites though some, that is, quercetin glycosides, may yield as many as 20 metabolites.[34] The flavonol quercetin occurs in fruits and vegetables with a particularly high concentration in onions. Anthocyanins are present in fruit where they are responsible for red, blue, and purple colors. The flavan-3-ols ()-epicatechin and (þ)-catechin are also present in fruits, cocoa, and green tea.[22, 35]

2.3. Polyphenols Tissue distribution, Drug disposition effects on Bioavailability

The tissue distribution of the polyphenols has been studied mainly from rodent studies, but differences between the human and animal genomes may also lead to potential problems of extrapolation.[25,36] Another challenge to the validity of animal study is that rodents methylate dietary phenols far more extensively than humans. Most of the data published from humans' studies on the bioavailability refer only to the release of the polyphenols from the food matrix and their consequent absorption (i.e. concentration in the blood or in the urine).[9] The determination of the bioavailability of the polyphenols in target tissues is obviously much more important than the knowledge of their plasma concentrations. Another challenge of methodological difficulty lies in the fact of difficulty in choosing the key active metabolite for study.[7,37]

The determination of the actual bioavailability of polyphenol metabolites in tissues is much more important than having an understanding of their plasma concentrations.[6] The kinetics of penetration and elimination of polyphenols in the tissues seems less reported and may well represent an emerging area of research interest.[38]

2.4. Effect of Absorption and metabolism on Bioavailability of phytochemicals

Polyphenols are known to undergo major modification during absorption. Glycosides may be hydrolyzed to aglycone in the small intestines or in the colon, then end up in the liver through the portal circulation. Transport across the gut mucosa often take place through an active transport mechanism.[16,38] Hepatic metabolism enhances conjugation (and solubility/serum availability) by methylation, sulfation, or glucuronidation. This promotion does not mean that polyphenol metabolites are free in the blood. Studies show that binding of metabolites to plasma proteins is the predominant mode of distribution. High affinity for albumin and marked hydrophilicity vary with specific chemical structure.[39]

Although solubility is not an issue for most polyphenols research shows that lipophilic compounds such as carotenoids, phytosterols, and triterpenes require emulsification/micellization prior to their absorption and uptake.[23,40] It is also noted that micelle size, shape, constituents, and macronutrient environment has not well documented and mechanism not well understood. The relevance and specific types of interaction with brush border enzymes, transporters, and subsequently with colonic microflora has not been well understood. Some polyphenols, such as, quercetin, are able to interact directly with lipid membranes. Most polyphenols at physiologic pH, and at nutritional doses, form hydrogen bonds with the polar head groups of phospholipids at the membrane surface.[27,41]

2.5. Influence of environmental factors on bioavailability

Generally, the conditions under which plants are cultivated, period of harvest, environment and cultivars have an impact on bioavailability of the fruits of harvest. Exposure to sunlight, wavelength of light in artificial environments, pH of the soil, constituents and degree of fertilizer use, degree of ripeness at harvest, and morphological source, that is, stem, leaf, flower, or fruit, all have impacts on character of nutrients and their bioavailability.[5,42]

2.6. Effect of Food processing factors on bioavailability

Food treatment such as Thermal, homogenization, lyophilization, cooking (boiling, frying, steaming), storage, mechanical treatments, such as, grating, cutting, chopping, slicing, mashing, and juicing to release components from disrupted tissue matrix, may have significant effect on the bioavailability of nutrients from enzyme activation (i.e. polyphenol oxidase and alliinase).[3,19,43] The impact of mild to. moderate heat or cooking; thermal and nonthermal processing, and cooking methods can lead to a staggering variation in the bioavailability of the spectrum of polyphenols. At lower level heat, carotenoids decrease but increases with elevated heat.[2,15] Reports are available on examples of reduction in total phenolic content with heat, reduced antioxidant activity in beans.[44] Other reports show a significant increase in antioxidant activity in another species of beans such as *Phaseolus vulgaris* L, cooked at 121ºC.[13] Some researchers observed that total phenolic content and antioxidant activity in other species of beans actually increased following the application of heat.[21] Generally, storage affects the content of polyphenols, but with a few notable exceptions, storage of any kind, including refrigeration results in a decrease in phenolic compounds. This is true for most fruits, vegetables, wines, and olive oils.[26,45]

3.0. HOST FACTORS IN BIOAVAILABILITY

Human host physiology and metabolism show high level of complexity and highly diversified within a subject temporally and between subjects as a function of many variables: such as;

Fed or fasted state of an individual, dietary load, source and food matrix, general health and state of gastrointestinal tract (ie rate of gastric emptying, motility status, time of day and life style factors, acute or chronic illness of the individual (example hepatic insufficiency and impaired renal function, pregnancy and status, if hospitalized.[2,9,15] For Chronic patients, the following can be considered postoperative status (example active recovery from surgical intervention and wound healing stage) anthletic status (example ongoing athletic training or weekend athlete), nutritive status (example malnutrition or nutrient insufficiency), age extremes (example generally, drugs are metabolized more slowly in foetal, neonatal and geriatric population.[16,17]

3.1. Food factors in bioavailability

The physicochemical dietary factors have a significant effect on the way in which the host processes micronutrients and also in the chemistry of digestion, absorption, and distribution. The presence and content of other nutrients; such as, high levels of zinc decrease Fe and Cu absorption; vitamin C, a potent reducing agent improves nonheme Fe absorption; and vitamin D improves Ca, P, and Mg transport and absorption.[13] Since carotenoids are fat soluble, the addition of small quantities of fat or oil can enhance bioavailability.[4,18]

The interactions with other drugs/foods, for example, antacids, alcohol, and nicotine; shows that inhibitory interaction effects can be nutritionally advantageous as in the case of dose-appropriate phytosterols that may be an adjunct for lowering the absorption of low-density lipoprotein cholesterol in patients with hyperlipidemia.[8,19] Interactions observed with other foods such as grapefruit juice, pomelo, cranberry juice, brassica vegetables via enzymatic inhibition can decreased the rate of metabolism, for example, the case of grapefruit juice that can inhibit CYP3A activity.

3.2. Food Supplement effects in bioavailability

Physical properties of a drug like hydrophobicity, pKa, solubility, particle size, and binding cation represent major factors, all of which influence bioavailability. The drug formulation and encapsulation, excipients used, manufacturing methods, immediate release, modified release, delayed release, extended release, sustained release, and the dosage form all contribute to bioavailability.[20] Apart from vitamin C, smaller doses of nutrients do appear to increase the percentage of nutrient absorbed. However, a modification of dosage form, does not necessarily affect the location of maximum absorption along the gastrointestinal tract. Water-soluble nutrients, both vitamin C and mineral salts initially appear to be absorbed quite rapidly and in the case of mineral salts, most notably zinc, a delay appears before a second phase of absorption occurs later along the gut.[6,21] The lipophilic nutrient, carotene, appears to be more slowly absorbed, but this reflect the time needed to produce an emulsified or protein-bound form compatible with transport into the serum, thereby facilitating bioavailability. The reduced bioavailability of carotene and vitamin E in soft gel form may also be related to competition with the vegetable oil-based vehicle, present in excess, for emulsification by chylomicrons integral to absorption.[7,22] This is in contrast to the normal expectation of the impact of oil-based delivery in the presence of an emulsifier.

Generally, micronutrients that are intrinsic to food and those that are delivered through supplements have variation in bioavailability that are controlled by complex processes and interactions. These interactions are grouped under Absorption, Distribution, Metabolism, and Excretion (ADME) model, which was developed to facilitate the characterization of the pharmacokinetics of drugs and phytochemicals. Unlike most drugs, micronutrients may not act efficiently in isolation but in association with bioactive compounds in the food matrix to produce synergistic activities.[4,13,23]

4.0. THE EFFECT OF DRUG DELIVERY SYSTEMS IN INCREASING BIOAVAILABILITY

Clinical medicine uses many pharmaceutical products for therapeutic use, and the list has increased significantly with greater understanding of molecular mechanisms of diseases. However, favorable drug action alone against the disease is not sufficient to meet the need of the medical community; in addition, avoiding undesirable drug actions on normal tissues, as well as minimizing side effects of the therapy, is equally important. Clinically, the therapeutic efficacy of a phytochemical depends not only on its intrinsic pharmacological activity but also on the bioavailability at the target site.[11,47]

Many agents have low aqueous solubility, and this is associated, in general, with low oral bioavailability.[42] In the development of new chemical entities, the ability to develop a suitable pharmaceutical formulation for delivery is very important, and therefore the means of delivering phytochemicals are critical for effective prevention and treatment of diseases. The emergence of new technologies has generated lots of interest in developing novel drug delivery systems to advance both the pharmacological and therapeutic properties of parenterally administered drugs.[48] A promising strategy to overcome low bioavailability and systemic toxicity challenges is the application of drug-loaded nanosized drug carriers, such as polymeric nanoparticles (NPs), liposomes, dendrimers and micelles.[43,44] The use of these carriers has several advantages when compared to systemic chemotherapy.

4.1. Potential effect of Nanocarriers to enhance drug bioavailability

Cancer therapies are currently limited to surgery, radiation, and chemotherapy. All three-methods risk damage to normal tissues or incomplete eradication of the cancer. Nanotechnology offers the means to target therapies directly and selectively at cancerous cells through; Nanocarriers, Passive Targeting, Active Targeting and Destruction from within.[3,11] Conventional chemotherapy employs drugs that are known to kill cancer cells effectively, but these cytotoxic drugs kill healthy cells in addition to tumor cells, leading to adverse side effects such as nausea, neuropathy, hair-loss, fatigue, and compromised immune function.[5]

Nanoparticles can be used as drug carriers to enhance bioavailability for chemotherapeutics to deliver medication directly to the tumor while sparing healthy tissue. Some Nanocarriers have several advantages over conventional chemotherapy in the following way;

i) Nanoparticles can protect drugs from being degraded in the body before they reach their target, can also

enhance the absorption of drugs into disease and into the cancerous cells themselves.
ii) They can allow for better control over the timing and distribution of drugs to the tissue, making it easier for clinicians to assess how well they work.
iii) Nanocarriers can prevent drugs from interacting with normal cells, thus avoiding side effects. iv) Nanocarriers can modulate the pharmacokinetics of existing drugs, and it may be useful to increase delivery of anticancer agents to target sites

A well-documented nano carrier system of nanosphere, nanocapsule, dendrimer, polymeric micelles, liposome, solid lipid nanoparticles (SLN), are illustrated in figure 3.

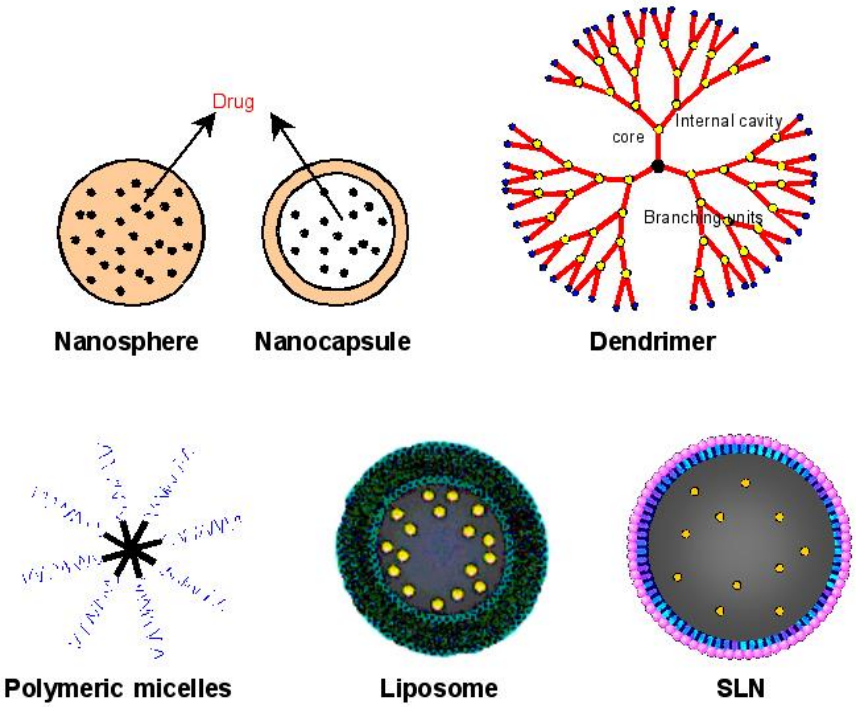

Figure 3: Nanotechnology Based Drug Delivery Systems for Cancer Therapy (SLN=solid lipid nanoparticle).[25]

Some of the drug delivery methods that have already made a significant impact either by enhancing delivery of the drug to its target tissue or increasing its bioavailability by many folds includes;

4.2. Nanoparticles

A lot of research interest has gained momentum in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. NPs range in size from 10 to 1000 nm and can be synthesized from lipids, proteins and carbohydrates, as well as several natural and synthetic polymers.[49] For nanoparticle delivery, a drug is dissolved, entrapped, encapsulated or attached to a nano particle matrix. Based on the method of preparation, NP, nanospheres or nano-capsules can be obtained and are now exploited for a series of biomedical applications.[50] The use of nanoparticles is useful to improve the therapeutic index of encapsulated drugs either by protecting them from enzymatic degradation[45], altering pharmacokinetics[46], reducing toxicity[47] or providing controlled release over extended periods of time[48] has gained enormous acceptance of NP systems in the last decade.[51].

NPs may enhance the oral bioavailability of poorly soluble drugs and the tissue uptake after parenteral administration, through adherence to the capillary wall. They also enhance the delivery of some drugs across the cell membranes. Based on their small size, NP have the potential to leave the vascular system and enter sites of inflammation.[49,52] The NP size limitation for crossing different biological barriers is dependent on the tissue, target site and circulation.[50] NPs are subject to phagocytosis and endocytosis and due to their hydrophobic surface, they are rapidly opsonized (coated) by plasma proteins and taken up by the mononuclear phagocytic system (MPS), that are found in organs such as liver, spleen and bone marrow.[52] In addition, coating with polyethylene glycol (PEG) or hydrophilic copolymers results in increased hydrophilicity, which allows prolonged circulation in the bloodstream and thus greatly enhanced uptake in non-MPS organs and accumulation at sites of inflammation.[49]

There are several kinds of NP used in drug delivery systems such as the self-assembled NP that are generally characterized by a hydrophobic core and hydrophilic shell. They are considered as superior drug carriers and have been developed by several research groups.[51,52] A

second kind of NP is the polymeric NP, which may be synthesized by various methods[53], according to needs of the application and type of drug being encapsulated. Polymeric NPs have properties of controlled/sustained release, subcellular size and biocompatibility with tissue and cells.[54] Solubility and pharmacokinetic properties of drugs may be improved by encapsulation within NPs. This delivery approach could enable further clinical development of chemical entities that have stalled because of poor pharmacokinetic properties.[55] Several researchers have used different types of NP for chemoprevention by narigenin[56], curcumin[57] and epigallocatechin gallate.[58,59]

Nanodrugs are stable in blood, non-toxic, non-thrombogenic, non-immunogenic, noninflammatory, do not activate neutrophils, are biodegradable and applicable to delivery of various types of molecules, such as drugs, proteins, peptides or nucleic acids.[60] Stimuli-responsive polymer-based NPs have received a lot of interest in areas of drug and gene delivery, tissue engineering and biosensors.[61,62] Such NPs can undergo abrupt physical or chemical changes in response to change of environmental conditions, such as pH, temperature, light, magnetic field or glucose.[63,64] More recently some studies have reviewed biologically responsive polymeric NPs for drug delivery that release their drug cargo in response to a change in pH or oxidative stress.[65] These reviews have been of significant clinical interest as they offer the opportunity to link drug delivery to a specific location or disease state. One example is paclitaxel (PAC) delivery by loading on pH-responsive NPs. This system has been tested against MDA-MB-231 human breast cancer cells *in vitro* and has demonstrated superior cytotoxicity when compared to PAC delivery on non-responsive polycaprolactone (PCL) NPs.[66] In another study, paclitaxel (PAC) delivery on pH-responsive NPs demonstrated a greater efficacy *in vivo* against subcutaneous SKOV-3 tumors compared to free PAC. The SKOV-3 is an ovarian cancer cell line derived from the ascites of a 64-year-old Caucasian female with an ovarian serous cystadenocarcinoma. The SK-OV-3 cell line is also hypodiploid, with a modal number of chromosomes of 43 (range 42-45), occurring in 63.3% of cells.[67] There are different school of thoughts among scientists that the use of the full potential of nanotechnology needs some consideration to safety issues especially as there is limited experimental toxicity data available on the vast range of NPs. Long term use of nanoparticles could lead to potential risk for toxicity as one of the primary mechanisms of nanoparticle toxicity is production of reactive oxygen species (ROS) and free radical due to foreign body reaction which can lead to oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA.[68,69] NP-induced oxidative stress can occur during the dissolution of iron-based NPs, which catalyzes ROS generation and formation of OOH· and OH· radicals from hydrogen peroxide (H_2O_2) via the Fenton reaction.[69,70] Some studies have suggested that NPs are not inherently benign and can affect biological behaviors at the cellular, subcellular, and protein levels.[71,72] Although polymeric NPs is well appreciated in the biological point of view, it has been reported to trigger detrimental responses. Nanopolymers made of silica dioxide have been shown to increase the kidney weight and creatinine levels when given intraperitoneally at 200 mg/kg body weight in *in vivo* animal model.[73]

Another major challenge for biodegradable polymeric nanoparticles is the association with solvent residues and polymer toxicity. NPs derived from different materials like copper[74], silica[75], TiO2[76], gold[77], silver[78] and polystyrene[79] have been reported to show potential toxicity in murine models when delivered orally or by intravenous route of administration. However, NPs formed from biodegradable materials such as poly (lactic-co-glycolic acid) (PLGA)[80] and polycaprolactone (PCL)[81] are expected to demonstrate none or fewer toxic effects than nonbiodegradable materials.[69,70]

4.3. Liposomes

Liposomes are nano-size artificial vesicles of spherical shape that can be produced from natural phospholipids and cholesterol. These vesicles have been shown to serve as immunological adjuvants and drug carriers.[82,83] Although liposomes can vary in size from nanometers to tens of micrometers, it generally ranges from 25 nm to 2.5 μm.[84] The main advantages of liposomes are their ability to encapsulate various materials and their structural adaptability is due to the fact that liposomes can encapsulate drugs with widely varied solubility or lipophilicity, either entrapped in the aqueous core of the phospholipid bilayer or at the bilayer interface.[84]

Table 1: Advantages and disadvantages of liposome.[19]

Advantages of liposome	Disadvantages of liposome
Liposomes increased efficacy and therapeutic index of drug (actinomycin-D)	Low solubility
Liposome increased stability via encapsulation	Short half-life
Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and nonimmunogenic for systemic and non-systemic administrations	Sometimes phospholipid undergoes oxidation and hydrolysis-like reaction
Liposomes reduce the toxicity of the encapsulated agent (amphotericin B, Taxol)	Leakage and fusion of encapsulated drug/ molecules
Liposomes help reduce the exposure of sensitive	Production cost is high

tissues to toxic drugs	
Site avoidance effect	Fewer stables
Flexibility to couple with site-specific ligands to achieve active targeting	

Despite the many advantages of liposomes, including safety and biocompatibility potential, their main challenge as nanocarriers is that they are not stable in plasma.[92] On intravenous liposome administration, selective serum proteins (opsonins) bind to their surface, thus signaling their presence. After signaling, the liposomes are then rapidly captured by the mononuclear phagocyte system (MPS) and removed from the blood circulation. This very behavior has been exploited for efficient delivery of antiparasitic and antimicrobial drugs to treat infections localized in the MPS.[93,94] However, when the target site is beyond the MPS, the use of liposomes that are able to evade this system is required to reach longer circulation times. Studies have shown that prolonged circulation time of liposomes may result in significant accumulation in highly vascularized, permeable tissues such as tumors[95], especially in cases involving active neo-angiogenesis. Tumor localization of long-circulating liposomes, such as PEG-coated (pegylated) liposomes, has a passive targeting effect that may allow large accumulation of encapsulated drug in interstitial fluid at the tumor site.[96] It is on this basis or rationale that pegylated liposomal doxorubicin delivery for cancer therapy can be achieved. In this formulation, PEG coating protected the liposomes from opsonization and recognition by the reticulo-endothelial system, which resulted in prolonged circulation time, and enhanced accumulation in tumors.[97] Preclinical experiments indicate that stealth liposomal delivery of anthracyclines decreases the cardiotoxic effect, enhances antitumor activity, and improves the overall therapeutic index.[98]

4.4. Nanoshells

Developed by Drs. Naomi Halas and Jennifer West – Rice University 1994. Nanoshells have a core of silica and a metallic outer layer. These nanoshells can be injected safely, as has been demonstrated in animal models. Because of their size, nanoshells will preferentially concentrate in cancer lesion sites. This physical selectivity occurs through a phenomenon called **enhanced permeation retention (EPR).** Nanoshells can be further decorated to carry molecular conjugates to the antigens that are expressed on the cancer cells themselves or in the tumor microenvironment.

This second degree of specificity preferentially links the nanoshells to the tumor and not to neighboring healthy cells. Moving away from conventional chemotherapeutic agents that activate normal molecular mechanisms to induce cell death, researchers are exploring ways to physically destroy cancerous cells from within using the nanoshells technology in the laboratory to thermally destroy tumors from the inside.

Nanoshells can be designed to absorb light of different frequencies, generating heat (hyperthermia). Once the cancer cells take up the nanoshells (via active targeting), scientists apply near-infrared light that is absorbed by the nanoshells, creating an intense heat inside the tumor that selectively kills tumor cells without disturbing neighboring healthy cells. Similarly, new targeted magnetic nanoparticles are in development that will both be visible through Magnetic Resonance Imaging (MRI) and can also destroy cells by hyperthermia.

Nanoshells are used in fighting cancer cells as indicated in figure 3

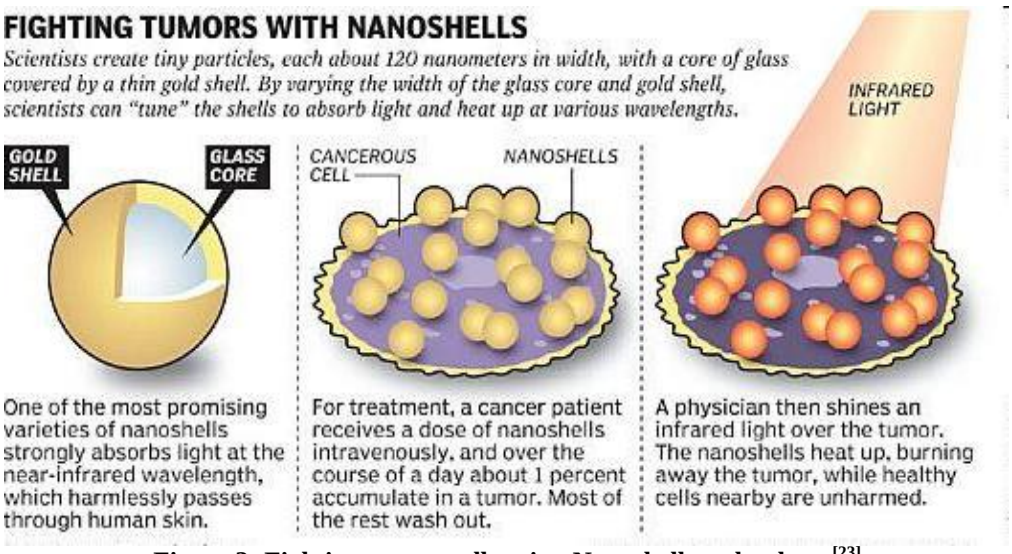

Figure 3: Fighting cancer cells using Nanoshells technology.[23]

4.5. Micelles

Micelles are lipid molecules that are arranged in a spherical form in aqueous solutions. Polymeric micelles range from 10 to 100 nm in size, and they are usually very narrow.[51] The critical association concentration of polymer is lower by several orders of magnitude than typical critical concentration values for surfactant micelles, which makes polymeric micelles more stable toward dilution in biological fluids. Micelles can increase drug bioavailability and retention, since the drug is well protected from possible inactivation by its micellar surroundings.[99] Drug release from micelles are characterized by many factors, such as micelle stability, rate of drug diffusion, the partition coefficient and the rate of copolymer biodegradation.[100] The drug concentration within the micelles, the molecular weight, physicochemical characteristics of the drug and its location within the micelles can also affect drug release.[101] Drug release from the appropriate types of micelles can be enhanced in the targeted area by certain physical factors or stimuli, such as pH, temperature, ultrasound and light.[102]

So far known, polymeric micelles designed from amphiphilic block copolymers have been found to hold a significant potential as drug delivery vehicles for a variety of anticancer drugs due to unique properties, such as high solubility and low toxicity.[53] Apart from improving drug solubility, small particle size, long circulation, targeting and easy production properties, polymeric micelle systems can alter the drug internalization route and subcellular localization. They can also reduce the P-glycoprotein efflux effect and, consequently, exert a different mechanism of action from the entrapped drugs.[54] They also have physicochemical properties for tumor targeting by an enhanced permeability and retention effect that is a type of passive targeting mechanism, leading to a higher drug concentration at the tumor site and decreased side effects compared with systemic administration.[88] In comparison with more recent nanodrug delivery systems, including liposomes, NPs and dendrimers, polymeric micelles possess higher drug-loading capacity as well as improved stability.[72]

4.5. Niosomes

Niosomes are microscopic lamellar structures, which are formed on the admixture of nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol, with subsequent hydration in aqueous media.[83] They resemble liposomes in their architecture and can be used as an effective alternative to liposomal drug carriers.[74] Niosomes are a promising vehicle for drug delivery, and since they are non-ionic, they are less toxic and improve the therapeutic index of drugs by restricting their action to target cells. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, trapped volume, surface charge and concentration can control vesicle characteristics. The vesicles may act as a depot, releasing the drug in a controlled manner. Niosomes are osmotically active, stable and increase the stability of the entrapped drug. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration.

Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in an external non-aqueous phase. Niosomes have been proposed for a number of potential therapeutic applications, i.e., as immunological adjuvants[75], anticancer and anti-infective drug targeting agents[77], carriers of anti-inflammatory drugs[78] and as diagnostic imaging agents.[114] In addition, niosomes are versatile carrier systems and can be administered through various routes. Particular efforts have been aimed at using niosomes as effective transdermal drug delivery systems.[119,120]

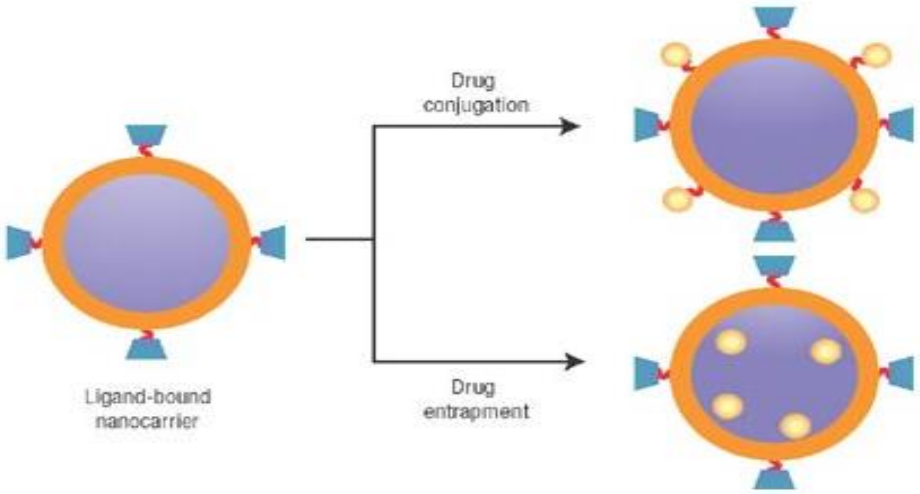

Figure 4: Schematic diagram of the drug conjugation and entrapment processes. The chemotherapeutics could be bound to the nanocarrier, as in the use of polymer–drug conjugates, dendrimers and some particulate carriers, or they could be entrapped inside the nanocarrier.[41]

4.6. Implant delivery system

Implants of drug-loaded polymers, either as milli rods, pellets or microspheres, are capable of delivering drugs for prolonged periods. The benefits of this subcutaneous implantation include greater assurance of patient compliance, which can lead to better therapeutic outcome, particularly for chronic medication. This approach is well recognized for contraception and hormonal therapy.[102] Two types of polymeric delivery systems are being used: nondegradable and biodegradable polymeric matrices.

Non-degradable biomatrices are composed of either silicon or poly (ethylene-co-vinyl acetate).[93] The Norplant delivery system uses this approach for contraception.[84] Other scientists have used the system to deliver ellagic acid in a mammary tumorigenesis model and shown effectiveness while delivering 130-fold less compound via silastic implants compared to dietary route (500 ppm), during a 28-week treatment period.[135] Although this approach has the potential to deliver over prolonged time periods, risks include mechanical failure that may lead to dose dumping, in the case of reservoir systems, and continuous dose drops, in the case of solid-drug distributed matrices. The other issue related to this system is the potential for fibrous growth around the implants, sometimes making it difficult to remove them at the end of the treatment period.

4.7. Cyclodextrin

Cyclodextrins (CDs) are unique molecules with 'pseudo-amphiphilic' structure, and several members of this family are used industrially in pharmaceutical and biomedical applications. The enzymatic degradation of starch by glucosyltransferase generates cyclic oligomers of α-1,4D-glucopyranoside, or CDs. CDs with lipophilic inner cavities and hydrophilic outer surfaces are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes.[92] CDs have an internal hydrophobic domain that can accommodate poorly water-soluble molecules, while the outer hydrophilic surface facilitates its solubility in the aqueous environment.[95] They have been widely exploited for drug delivery and used in the preparation of various delivery vehicles, such as liposomes, microspheres, microcapsules and NPs.

CDs enhance bioavailability of insoluble drugs by increasing drug solubility and dissolution. They also increase the permeability of insoluble, hydrophobic drugs by making the drug available at the surface of the biological barrier (e.g., skin and mucosa) from whence it partitions into the membrane without disrupting the lipid layers of the barrier. In such cases, it is important to use just enough CD to solubilize the drug in the aqueous vehicle since an excess may decrease drug availability.[124] Cyclodextrins can also enhance drug bioavailability by the stabilization of drug molecules at the bio-membrane surface. For example, CD-enhanced insulin bioavailability after nasal administration is partly due to this stabilizing effect.[125] Sublingual drug delivery is one of the most efficient ways to bypass hepatic first-pass metabolism[126], whereby the drug enters the systemic circulation by dissolving in the mucosa. In the sublingual formulations, the complexation of poorly water-soluble drugs with cyclodextrin has been shown to increase the bioavailability of various lipophilic drugs.[127]

4.8. Potential approved nano cancer drugs

Some potential approved cancer drugs are now well documented as the case of doxil approved for ovarian cancer AIDS-related Kaposis Sarcoma shown in figure 5.

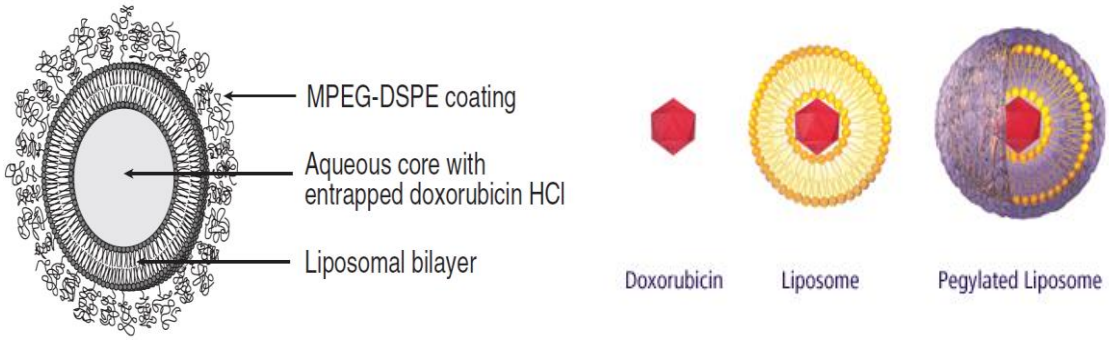

Figure 5: Doxil approved for Ovarian Cancer AIDS-related Kaposi's Sarcoma multiple Myeloma.[25]

The STEALTH® liposome methoxypolyethylene glycol (mPEG) containing Antitumor antibiotic interferes with cell division. It has a half-life of 55 hours in humans, 100 nm size, produced by Ben Venue Labs, in Bedford, United Kingdom.

CONCLUSION

The effect of absorption enhancing effects of natural products has been developed in this paper. Phytochemicals, food supplements, micronutirents and many related compounds have been reported to contribute to the enhancing of co-administered drugs with significant enhancing therapeutic activities. In most situations, bioavailability enhancing potential of natural compounds could be attributed to inhibition of P-gp and oxidative metabolism with minimal toxic effects. Coadministration of natural compounds is shown as one

of the promising approaches to enhance the absorption and bioavailability of drugs.

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Authors' contributions

This work was carried out in collaboration among all authors. Authors FCN, ETF, NS designed the study. Authors DJF, MG, MEB, KNK NV, TPM did data mining and organization. Authors LBF, BEE, and ZNI sorted information and wrote the first draft. All authors read and approved the final draft

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