

REVIEW ARTICLE

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Dietary Polyphenols in Human Health: A Novel Critical Review of Benefits and Possible Risks

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Abstract

Efforts are underway globally to eradicate malnutrition by encouraging optimal growth and health. Certainly, one of the main essential components of long-term, excellent health is food. Natural polyphenols possess a diversity of positive health advantages and are a significant part of foods produced from plants. They may be regarded as non-essential nutrients. However, polyphenols may also have negative consequences, regardless of the circumstances, dosage, and relations to the environment, just like any other molecule. Polyphenols' biological properties and their possible application in disease prevention are examined. The study examined the mutagenic, carcinogenic, and genotoxic properties of polyphenols, as well as their prooxidative activity. The current study describes the potential adverse consequences of consuming polyphenols, particularly through supplements, and delivers an in-depth examination of the recent research regarding the detrimental impacts of polyphenols on human health. Consuming foods rich in bioactive compounds reduces the probability of growing several persistent medical conditions, which are the primary contributors to premature death and disability globally. It is essential that the importance of public education regarding the application of various polyphenols and their effects, including their adverse effects in today's society, be emphasised.

Keywords: Adverse Effect, Biological Properties, Moderation, Nutrients, Preventing Diseases

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Abbreviations: WHO - World Health Organization; NCD - Noncommunicable diseases; ICN2 - Catalan Institute of Nanoscience and Nanotechnology; UV-B - Ultraviolet B radiation; SET - Single-electron transfer; HAT - Hydrogen atom transfer; EGCG - Epigallocatechin gallate; DNA - Deoxyribonucleic Acid; POP - Pelvic organ prolapse; GTE - Green Tea Extract.

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INTRODUCTION

By guaranteeing optimum growth and health from an early age. The World Health Organization (WHO) seeks to eradicate malnutrition from society. On May 28, people commemorate World Nutrition Day. In an effort to combat all forms of hunger, the UN General Assembly acknowledged the 2016-2025 a Decade of Efforts towards Enhancing Nutrition. In order to accomplish global nutrition goals and food-related NCD targets, this decade describes the application of decisions made at the Second International Conference on Nutrition (ICN2). An enormous amount of success was achieved by the 17th World Congress on Polyphenol Applications, which was held in Milan, Italy.^{1,2}

The phenol contains a hydroxyl group attached to an aromatic benzenoid ring; polyphenols and polyhydroxyphenols are identical in nature. Since 1894, the term “polyphenol” has been in use. Concentrated tannins, which are plentiful in leaf tissues, the epidermis, bark layers, flowers, fruits, and other plant tissues, are the most plentiful type of polyphenol. The global epidemic of malnutrition has significant and long-lasting impacts on individuals and their families, as well as on communities and countries, in the areas of development, economy, social concerns, and medicine. Extreme and pervasive malnutrition is the cause of these consequences. These consequences may be observed in the areas of development, economy, social services, and medical. Many naturally occurring plant kingdoms have polyphenol groups, which are composed of numerous hydroxyl radicals on aromatic rings. As a result, several researchers have investigated and written about a variety of phenolic compounds. Polyphenols are frequently found in nature as conjugated structures, which bind the number of sugars the leftovers to a phenol hydroxyl group. However, right away interactions between the sugar component and an aromatic carbon atom are also feasible. Polyphenols are biologically active, with antioxidant, anti-inflammatory, and anti-cancer properties. Polyphenols are a key source of anti-infective chemicals that can aid in the treatment of antibiotic-resistant illnesses in humans because they kill microorganisms and inhibit cyst formation. When it comes to

antioxidants, polyphenols are the most prevalent in a man's eating routine. In recent years, several research have been undertaken to evaluate the physiological behavior of dietary components with functional properties and bioactives derived from food. Consuming foods rich in bioactive components reduces the risk of acquiring a variety of chronic illnesses, which are the leading causes of death and morbidity on a worldwide scale.³⁻⁵

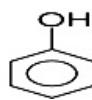
The categorizing for distinct polyphenols

It is necessary to classify these polyphenols into the following four categories: phenolic acids, flavonoids, stilbenes, and lignans. One of the distinguishing characteristics of phenol is that it consists of an aromatic benzenoid ring in addition to a hydroxyl group. Figure 1 represent the different kinds of polyphenols with their structure.⁶

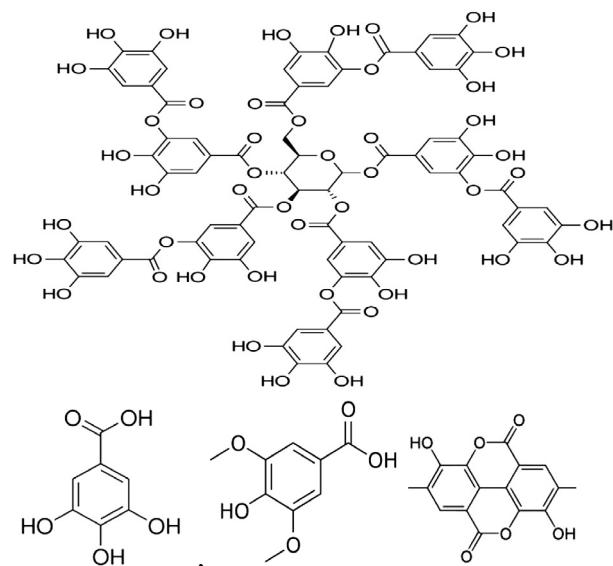
Nutritional products that are high in polyphenols

Over eight thousand distinct numerous polyphenol kinds have previously been discovered. Foods contain polyphenols in both bound and free forms. Free polyphenols were easily extracted, and their antioxidant capacity could be accurately measured, unlike insoluble polyphenols. Coffee, berries, dark chocolate, cocoa powder, olive oil, and a number of spices and seasonings, including cloves and star anise, are the main foods that contain high levels of polyphenols. Researchers discovered numerous polyphenolic components in honey, such as flavonoids and phenolic acid, and concluded that polyphenols in natural honey are good for people. Flavonoids and phenolic acid reduce oxidation and free radicals. Although different types of honey have different proportions of the healthy flavonoid and phenolic acid components, they all have similar identities. The kind of olive oil that has been subjected to the smallest degree of processing is known as extra-virgin olive oil. It is comprised of a diverse assortment of polyphenolic chemicals that are taken from the olive fruit. Phenolic molecules are capable of performing a wide variety of biological functions, ranging from those that stabilize auto-oxidation to those that improve human health. A few of these very best foods high in polyphenols that should be a regular part of your diet are listed in Table 1.⁷⁻¹¹

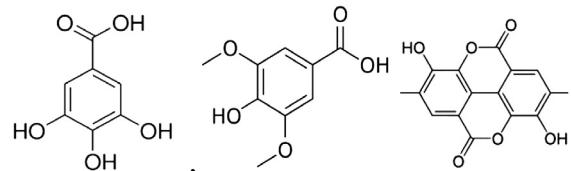
Structure of Phenol



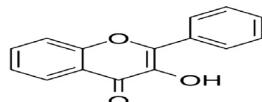
The structures of Tannins



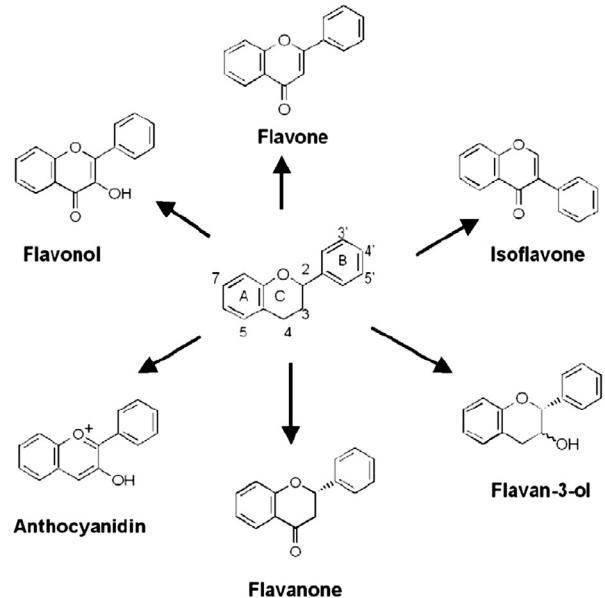
Vanillic acid, Syringic Acid, and Gallic Acid



The structure of Flavanols



Flavonoids are characterized by their structure



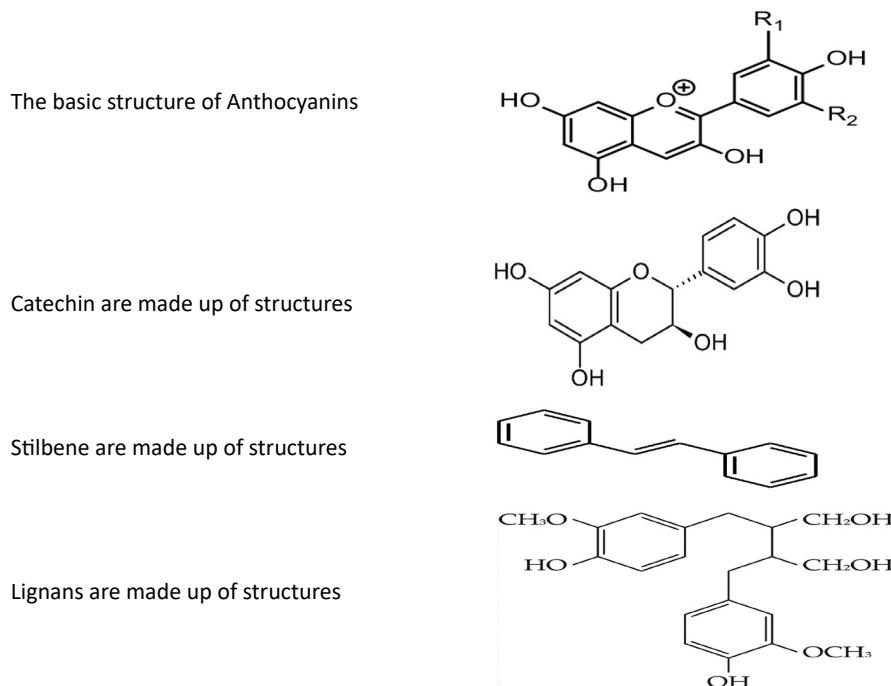


Figure. Different kinds of polyphenols with their structure

Why polyphenols are produced by plants

Green plants may be among the best chemists in the natural world, given the enormous number of compounds that have been discovered and identified from the Kingdom Plantae and the possibility that many more will be discovered in the future. Green plants generate phytochemicals through a range of metabolic and biochemical processes. In addition to their color, taste, and fragrance, phytochemicals can also have antinutrient or phytonutrient qualities. Antinutrients are phytochemicals that prevent the body from absorbing nutrients, whereas phytonutrients give green plants their therapeutic and health benefits. Plants are protected from UV-B radiation, which causes significant harm, as well as from diseases, insects, and herbivores by a variety of toxic phytochemicals. The evolution of early terrestrial plants was essentially determined by these substances. Tannins and phytate are two examples of antinutrients that have been found to have beneficial impacts on human health. Polyphenols, or “plant phenol”, are members of the phytonutrient family. Plant development,

regulation, and structure are influenced by polyphenols, which vary in kind and structure among taxa. To withstand environmental stresses such as heat, radiation, drought, salt, floods, etc., plant species modify the structure of their polyphenols. It is possible that polyphenols can regulate auxin and other plant growth hormones. Polyphenols increase plant pigments and offer UV-B protection.^{12,13}

Polyphenol has antioxidant effects

Free radicals are atoms or groupings of atoms that have one unpaired electron and can be formed chemically during the oxidation process. Because unpaired electrons tend to form pairs with other electrons, they are frequently extremely reactive and unstable. During metabolism in a live creature, an oxygen molecule (O_2) loses four electrons. The development of the reactive oxygen metabolites due to the fact that the process might be caused by electron excitation, energy addition, or interactions with the components of the transition's metals. It refers to these extremely reactive oxygen metabolites

as active oxygen species because of their strong reactivity with oxygen. The primary processes in live cells that generate free radicals include redox reactions, photolysis, radiolysis, and homolytic chemical bond fission. Within living things, free radicals initiate a chain reaction that can cause cell damage and consequently lead to a variety of diseases. In a living body, free radicals initiate a chain reaction, which antioxidants stop. To put it another way, antioxidants shield living things from the damaging effects of reactive oxygen species, or free radicals, by neutralising or deactivating their activity. Antioxidant chemicals are those that limit oxidation. Polyphenols, on account of the many functional groups, double bonds, and aromatic rings that they include, provide the ideal structure for performing the role of functioning as effective antioxidants. Polyphenols have the ability to seize free radicals such as hydroxyl radicals ($\bullet\text{OH}$) and radicals containing superoxide anion ($\text{O}_2\text{-}\bullet$). Furthermore, they have the ability to quench reactive oxygen species such as hydrogen peroxide (H_2O_2) and singlet oxygen ($^1\text{O}_2$) by means of electron donation (SET) or the transfer of hydrogen atoms (HAT). Polyphenols are supposed to be beneficial to people's health because of their antioxidant characteristics and their ability to dampen reactive oxygen species and free radicals. This is because polyphenols are believed to slow down the ageing process and prevent the onset of a variety of ailments. It is also possible for polyphenols to perform the role of co-antioxidants, which would be beneficial in the process of vitamin regeneration. A number of signalling pathways, such as energy metabolism, adipogenesis, antioxidant and anti-inflammatory responses in cells, are also regulated by them. They play a function in the regulation of these processes.¹⁴⁻¹⁹

Polyphenols' properties can affect their ability to produce antioxidants

The presence of polyphenols in foods is a well-established fact, wherever they can be made available for free or attached. The polyphenols' insoluble-bound antioxidant properties, that are mostly present in cereal grains and link with food matrix components such as protein and polysaccharide, could not be fully assessed using standard assays, influencing the test results. Free

polyphenols, on the other hand, were rather easy to extract and their antioxidant potential was accurately tested. The relationship between polyphenols' structure and activity has been thoroughly studied and recorded by the various workers. The structures, types, and locations of substituents in polyphenols affect their antioxidant efficacy. Phenolic hydroxyl groups play a major role in scavenging free radicals, but other groups, as well as their quantity and location, also play a significant role. Glycoside and methoxy groups, however, may be harmful. Furthermore, the degree of polymerization would affect the antioxidant capacity, which is typically advantageous. Polyphenols are easily lost because of their low stability. Their stability may be impacted by a few physical and chemical elements that are commonly encountered during processing, storage, and digestion, such as ascorbic acid, sugar, light, oxygen, pH, temperature, enzymes, and metallic ions. The antioxidant structure of polyphenols would be destroyed by degradation-induced link breakage. Consequently, one drawback was that polyphenols' poor stability would make it challenging for them to function as antioxidants under normal conditions. Bioavailability is the amount of active chemicals people can take in and use. The amount of polyphenols in your body determines how well they can protect you in real life. Four things often limit polyphenols bioavailability: Polyphenols are easier to absorb because they are hydrophilic. Adding a promoter to quercetin can make it easier to take and more effective. Polyphenols can't stay in their original form after being broken down by the bacteria in your gut. Instead, they only stay as chemicals. Recent research shows that polyphenols should be considered when figuring out how well they work. The gut bacteria biotransformation would change the polyphenols' natural structure, which would affect their antioxidant power. The ability of polyphenols to enter cells from the stomach and intestine is a key component of their bioavailability. The bioavailability of polyphenols is often less than optimum, which inhibits the antioxidant action of polyphenols in living organisms.²⁰⁻³⁴

The role of polyphenols in the management and preservation of disease

Polyphenols have the ability to avoid or

Table 1. Lists of the polyphenols found in foods that are regularly consumed throughout the day

1 Grains	Wheat, Rya, Oats, Whole
2 Fruits	Other examples of black fruits are black chokeberries, black and red currants, black elderberries, black grapes, blackberries, blueberries, apples, apricots, and black olives. Black chokeberries are also a kind of black fruit. Grapes, grapefruit, nectarines, peaches, pears, plums, raspberries, strawberries, and pomegranate are some of the fruits that are included in this category. Peaches and pears are also included.
3 Nuts	Various kinds of nuts and seeds, such as walnuts, chestnuts, hazelnuts, almonds, and flax seeds, among others.
4 Vegetables	There are a number of vegetables that are required to be included on the list. Some of these veggies are asparagus, broccoli, carrots, red chicory, red lettuce, onions, spinach, and shallots.
5 Beans	There are many different types of soy products, including but not limited to beans, sprouts, black beans, tempeh, tofu, white beans, soybean milk, soy yoghurt, and soya meat.
6 Beverages	Olives, rapeseed oil, olive oil, black tea, capers, coffee, dark chocolate, ginger, green tea, red wine, and red wine are some of the other ingredients that fall within this category. Vinegar made from cider.
7 Other items rich in polyphenols	Honey, dried herbs of basil, marjoram, and the following herbs are dried: parsley, peppermint, caraway, celery seed, cinnamon, cloves, and parsley. Pulverized cocoa, Cumin, and It is the curry powder. Chocolate in its darkest form, Spearmint, lemon, verbena, Mexican, oregano, rosemary, sage, and star anise seeds that have been dried.

minimize the signs of a wide range of metabolic diseases. This category includes the following conditions: cardiovascular illnesses (such as atherosclerosis, myocardial infarction, heart failure, also stroke); metabolic syndrome (as well as includes type 2 diabetes mellitus, central and abdominal obesity, systemic hypertension, and atherogenic dyslipidemia); the syndrome of metabolic syndrome. In addition to their antioxidant and antiplatelet characteristics, polyphenols also have powers. Polyphenols improve glucose homeostasis, lower blood pressure, and increase endothelial function by increasing HDL as well as inhibiting LDL oxidation. Studies conducted *in vivo* on rats have demonstrated that animals fed 10% hesperidin had lower plasma triglyceride levels than control. Furthermore, the fecal lipid content rose, preventing pancreatic lipase, even though hesperidin consumption had no effect on daily nutrient consumption, a growth in body weight, or an increase in productivity. When galangin was given to rats at a dose of 50 mg/kg for six weeks, there was also a notable decrease in serum lipid and lipid peroxidation. For instance, polyphenols' ability to inhibit pancreatic lipase may be advantageous in helping obese people lose body mass. Hypertension is one of the most harmful factors associated with deaths from cardiovascular diseases. Both black and green tea's polyphenols

dramatically reduce blood pressure. It is likely that tea polyphenols have a significant impact on reducing vascular inflammation, improving endothelial nitric oxide synthase activity, relaxing smooth muscle contraction, and preventing rennin activity as well as anti-vascular oxidative stress, even though the precise mechanism is unknown.

A polyphenol-rich diet or phenolic compound supplements have been shown to have positive effects on cognitive functions, amyloid diseases, including Alzheimer's and Parkinson's, and systemic and neurodegenerative diseases. Additionally, polyphenols are significant anti-cancer agents. Numerous animal models have demonstrated the potential of tea polyphenol compounds to prevent a wide range of cancers, including those of the ovaries, breast, pancreas, colorectal, esophageal, liver, lung, and kidney. There are a number of different mechanisms that polyphenols use in order to carry out their anticancer action. These mechanisms include the repression of angiogenesis, estrogenic and antiestrogenic activity, antiproliferation, stimulation of detoxifying enzymes, modulation of the immune system of the host, and anti-inflammatory activity. Other mechanisms include antioxidant and prooxidant activity, inhibition of certain protein kinases and other enzymes, and the subsequent changes in cellular signaling. Certain

polyphenols, such as quercetin, kaempferol, curcumin, resveratrol, and EGCG, have been shown to inhibit the expression of histone deacetylases. This suggests that these substances possess anticancer properties. They do this by repairing epigenetic changes that occur in cancer cells. Additionally, they may prevent healthy cells from developing into tumors through DNA methylation and histone modifications. Taking everything into account, polyphenols appear to be our best friend, supporting the healthy operation of our bodies. As a result, diets high in polyphenol compounds and dietary supplements that contain them have gained popularity. However, it is essential to keep in mind that the consumption of polyphenolic chemicals, especially when done so in big numbers and in a pure form (meaning that they are found in supplements rather than fruits and vegetables), may have negative effects or even be harmful to human health.³⁵⁻⁴⁶

Anti-Aging Effects of Polyphenols

One of the fundamental cornerstones of long-term, excellent health is surely food. Among the main goals for enhancing food quality have been directed and selected evolution through agricultural methods as well as experimental manipulation and alteration of dietary components. Finding natural substances that can prolong life, avoid chronic diseases, and improve health has attracted a lot of attention. In this context, it has been demonstrated that a variety of polyphenols, such as EGCG, curcumin, and quercetin, increase longevity. Some of the hallmarks of the Mediterranean diet include the consumption of foods derived from plants and olive oil, both of which have the potential to have positive impacts on one's health. As said by new research, the polyphenols found in olives and olive oil may help explain a number of the positive effects on health due to eating a Mediterranean food. Even in the event that the use of olive oil did not have an effect on the mortality rate, it is tempting to believe that the polyphenols found in olive oil would have the capacity to extend that life. In fact, there is growing evidence that the phenols in olive oil slow down the ageing process in people, animals, and cells.^{47,48}

Polyphenols pose potential risks to adverse outcomes of health

People prevent and treat a variety of illnesses by using polyphenols, a vital component of foods derived from plants that have many health benefits. A healthy diet has been shown to have protective effects against the toxicity. Unfortunately, depending on dosage, conditions, and environmental interactions, polyphenols can be hazardous, just like any other chemical. It has a protective effect primarily because of their effects on the antioxidant system's constituents, xenobiotic-elimination enzymes, and, consequently, reactive oxygen species (ROS) levels. Studies conducted on animals, both *in vitro* and *in vivo*, have shown that polyphenols possess qualities that are neuroprotective, hepatoprotective, nephroprotective, anti-inflammatory, and anticarcinogenic. Additionally, it avoids gonad toxicity and counteract immunosuppressive effects. Sometimes, a significant factor in the growth of sicknesses is nutrition.

Hormonal imbalance caused by polyphenols

Isoflavones, one type of polyphenol, have become well-liked as a substitute therapy for menopausal symptoms in women who are hormone intolerant. Because they can have both estrogenic and antiestrogenic effects in different tissues, isoflavones share structural similarities with estrogen. Due to the fact that only certain bacterial enzymes are capable of converting isoflavonoids, it is essential to bear in mind that the makeup of the microbiota in the gut is the primary factor that defines the biological activity of isoflavonoids. Genistein, for instance, may be transformed into p-ethyl phenol, while daidzein can be turned into its physiologically active metabolites, S-equol or O-desmethylangolensin. Both of these metabolites are examples of metabolites. Whereas isoflavones appear to benefit postmenopausal women, their effects on reproductive-age women may be less favorable. A placebo-controlled crossover study also documented the adverse effect of soy isoflavones. Additionally, it has been shown that isoflavones' estrogenic activity is safe or even helpful for women, but it can cause problems for men when

it comes to sexual activity. It has been proven that adult Sprague-Dawley rats who were given a diet that was high in phytoestrogens (an isoflavone content of about 600 µg/g) had considerably lower plasma levels of androstenedione and testosterone compared to rats that were fed a diet that was devoid of phytoestrogens.

So, are hormonal imbalances really a result of isoflavones? Generally speaking, it appears that isoflavones are not harmful to healthy individuals; however, this may not be the case for those who suffer from severe deficiencies or illnesses. In individuals with iodine deficiency, soy isoflavones have been shown in multiple studies to inhibit thyroid hormones. *In vivo* studies using rats have demonstrated that genistein can reduce thyroid peroxidase (TPO) by up to 80% in a dosage dependent way. In different works, the relationship between giving kids formula that contains soy and the onset of autoimmune thyroid ailment was examined. According to the authors, children with autoimmune thyroid disease were much more prone to fed soy-based milk formulas in their early years than both their siblings (frequency 31% vs. 12%, correspondingly) and kids in good health who are not related; the frequency is 13%. Thus, it was established that soy formula feedings during infancy were linked to autoimmune thyroid disease. The available findings from a variety of studies are unclear and frequently contradictory, to sum up. It is necessary to do more study in order to provide conclusive evidence about the safety of isoflavone usage, as well as to identify the subpopulations that these substances will have adverse effects on or that may be at risk.⁴⁹⁻⁵³

Potential adverse effects of polyphenol impeding iron absorption

The most vulnerable population for anemia is young children, since it is a severe public health concern, women who are pregnant or recently gave birth, teenage girls, and women who are menstruating, the World Health Organization (WHO) provides the following information. Countries with poor and lower-middle incomes have the highest rates of anemia prevalence, where it disproportionately affects people who live in rural areas, in households with lower incomes, and who have never attended school. It is estimated that thirty percent of women between

the ages of fifteen and forty-nine, thirty-seven percent of pregnant women, and forty percent of all children between the ages of six and sixty-nine months throughout the globe suffer from anemia. In the year 2019, anemia was responsible for the loss of fifty million years of healthy life due to the resulting impairment. The main causes were malaria, thalassemia and sickle cell trait, and dietary iron deficiency.^{54,55}

Iron insufficiency is a widespread condition that affects individuals all over the globe, despite the fact that it is present in the environment in significant amounts. For human existence, iron is a trace element that is absolutely necessary. Both a low intake of iron and its low bioavailability can contribute to a low body iron level within specific populations. The form of dietary iron affects its bioavailability. Hemoglobin and myoglobin from animal diets provide haem iron, whereas non-haem iron comes from plants and foods fortified with iron. A reduced bioavailability is associated with the latter, because intestinal absorption is much less efficient. By chelating the ions of transition metals (for example, Fe and Cu), polyphenols can prevent free radicals from forming in the Fenton and Haber-Weiss reactions. In addition to the polyphenolic compound's structure, the pH or ion form (Fe²⁺ vs. Fe³⁺ and Cu⁺ vs. Cu²⁺) affects the binding strength and the quantity of bound ions. Because it prevents the production of free radicals, this polyphenolic activity is thought to be good for the body. Furthermore, iron overload, a major risk factor for many illnesses, particularly chronic diseases in humans, is frequently treated with polyphenols due to their iron-chelating properties. But there are also negative consequences to this activity, like in people who are iron deficient. Anemia develops when polyphenols, which are abundant in a diet or when taken as supplements, bind to iron in the intestine and prevent it from being absorbed (Table 2). They may also have an impact on how iron homeostasis is regulated.⁵⁶⁻⁵⁹

Polyphenols' prooxidant activity and its effects

Polyphenols can be regarded as beneficial molecules, even though their prooxidative qualities are meant to kill cancer cells. However, the effects might not be desirable if polyphenols start to cause DNA damage and other oxidation of

Table 2. Polyphenol Hampering Iron Absorption some important results

Polyphenol	A potent inhibitors of iron absorption and Results	Ref.
Catechins (Present in teas)	<ul style="list-style-type: none"> In comparison to drinking water, the quantity of iron that was absorbed from a bread meal was lowered by fifty to seventy percent when the individual consumed drinks that contained twenty to fifty milligrams of total polyphenols per meal. Consuming drinks that had 100-400 mg of total polyphenols per serving, on the other hand, resulted in a reduction of 60%-90% in the amount of iron that was absorbed. Black teas (79%-94%), peppermint tea (84%), and chocolate (73%), and chocolate (71%), as well as the inhibitory effects of these substances, declined in a dose-dependent manner depending on the total polyphenol content. Responsible for supervising the administration of supplements to obese patients to obese patients in order to measure their body mass, lipid profile, elements, glucose level, and antioxidant status. For a period of three months, participants were given either 379 milligrams of GTE or a placebo on a daily basis. There was a substantial decrease in the amounts of triglycerides, cholesterol in general, low-density lipoprotein, total cholesterol, glucose, and iron in the blood was seen after receiving GTE therapy. This reduction was statistically significant ($p < 0.05$). Additionally, it was feasible to experience weight loss. The levels of high-density lipoprotein, zinc, and magnesium, on the other hand, all increased by a substantial amount. 	[60]
GTE stands for green tea extract.	<ul style="list-style-type: none"> Significantly restricted the passage of iron across the epithelium of Caco-2 intestinal cells when the concentration was at healthy levels. 	[61]
Grape seed extract (GSE), which has a high concen.	<ul style="list-style-type: none"> of polyphenols, and the polyphenol found in tea, known as (-)- epigallocatechin -3-gallate (EGCG), 	[62]
Quercetin	<ul style="list-style-type: none"> Bring down the quantity of iron that is unstable inside the cells. It has been shown that the complexes of quercetin and rutin with iron are able to pass through cell membranes. Free quercetin, on the other hand, was the only enzyme that was able to penetrate the cytoplasm and remove iron in cells. Both quercetin and a placebo capsule, each containing 500 milligrams, were administered to the patients twice daily for a period of twelve weeks, during which time their blood limits were monitored. In contrast to the placebo group, the ferritin level was found to be significantly lower ($p = 0.013$), whereas the number of entire red blood cells (RBC) was shown to be higher. Worker found inconsistent results in their study. After 20 days of eating 8 grams of raisins (<i>Vitis vinifera</i> L.), their iron and haemoglobin levels went up, ferritin levels went up, in addition, the levels of transferrin and total iron binding capacity (TIBC) decrease. 	[63]
Raisins (<i>Vitis vinifera</i> L.)		[58]
		[59]

normal cell components, which could ultimately result in mutagenesis. It is generally accepted that polyphenols are powerful antioxidants; nevertheless, under certain conditions, they are also capable of performing the role of prooxidants. Pure polyphenols are not the only substances that can function as prooxidants. Polyphenolic extracts made from the pomaces of Syrah and Chardonnay grapes or wines showed prooxidant activity. Their prooxidant action is predominantly catalyzed by transition metals such as iron and copper. They generate a redox complex with a transition metal ion or a phenoxy radical, which catalysis their prooxidant activity. After that, phenol radicals can react with oxygen to form a variety of reactive oxygen, that can cause lipid peroxidation, damage to DNA, or start the oxidation of other significant molecules. It has been demonstrated that certain polyphenols, particularly those containing small molecules like dihydroxy cinnamic acids, are readily oxidized and result in lipid peroxidation or DNA incision due to the activity of radicals created when Cu and oxygen are present. Therefore, more investigation is needed to determine the circumstances in which an antioxidant transforms into a prooxidant. Numerous studies have shown that various molecules containing polyphenols, for example ferulic acid, gallic acid, salicylic, syringic, vanillic, curcumin, catechin, ellagic acid, quercetin, and metal complexes of quercetin. Al, Zn, Ca, Cr, Mn, Co, Ni, Mg, As, and Cd are among the metals and metalloids that can catalyze these reactions including copper.⁶⁴⁻⁷¹

Polyphenols may be detrimental to cells, causing them to mutagenesis or having genotoxic and carcinogenic effects

Polyphenols may also interact with cell membranes to cause destructive effects on cells. There is a significant chance that polyphenols will have a harmful impact on cells because they can interfere with the function of membranes. Certain polyphenols' prooxidative activity and membrane-affecting properties may result in mitochondrial toxicity by lowering the potential of the mitochondrial membrane and pushing the cell into the apoptotic pathway. Although mitochondrial malfunction is linked to a variety of human conditions, including cancer, diabetes, obesity, and neurological diseases, problems

with apoptosis regulation may be a contributing factor in the development of cancer. Nevertheless, quercetin, which interacts with DNA, has the ability to disrupt cell cycles and, as a result, result in the regression of tumours. This is accomplished by activating the mitochondrial route of apoptosis. It was discovered by the researchers that acacetin, rhamnetin, apigenin, and morin were responsible for the instability of the membrane structure. This instability was created by the membrane lipids being disoriented, which ultimately resulted in induced leaking from the model vesicle. Naringenin and hesperidin also markedly enhanced the fluidity of model lipid membranes composed of dimyristoylphosphatidylcholine. This refers to the configuration of the polar heads of lipids was altered by both flavonoids; naringin had an ordering effect in the hydrophobic region, whereas hesperidin caused weak disorder. Additionally, naringin was more successful than hesperidin at altering the structure of the membrane. Certain polyphenolic compounds have the capacity to cause mutagenesis. The mutagenic and antimutagenic properties of 23 frozen fruit samples were examined in the study by the researcher. Acai, cashew apples, kiwi fruit, and strawberries all displayed mutagenic activity at all loci (Lys-revertant, His-revertant, and Hom-revertant) that were tested when they were studied in a haploid XV 185-14C strain of *Saccharomyces cerevisiae* cells. The findings obtained revealed that the pulps of these fruits exhibited mutagenic activity. The effect was dose-dependent and was seen at high levels of saturation (5%-15% [wt/vol]). The ability of polyphenols to cause chromosome damage or intercalate into DNA may also contribute to their carcinogenic effects.⁷²⁻⁷⁹ Those who take polyphenol-fortified supplements and meals should know their risks and possible negative effects on human health.

Polyphenols and their impact on drug metabolism

Reactive oxygen species and free radicals are both able to interact with polyphenols since they include a number of active functional groups, and several different kinds of chemicals. Polyphenol interactions with drug components significantly influence drug metabolism and pharmacokinetics, potentially enhancing or diminishing its beneficial effects. Consumers are often aware of interactions

of this kind; for instance, they are aware that it is not recommended to take pharmaceuticals alongside grapefruit beverages or infusions made from herbs. On the other hand, they have no idea of the underlying reasons behind such suggestions. Polyphenols and foods high in polyphenols, such as fruits, spices, and herbs, can change how drugs are absorbed, distributed, and metabolized. This is done by reducing P450 activity, which naturally affects how drugs work clinically, and by inhibiting P450 activity (competitive inhibition, non-competitive inhibition, and uncompetitive inhibition are the three primary types of enzyme inhibition). The concentration of a medication in the blood or tissues of the body rises when its metabolism is restricted, leading to a number of potentially quite harmful consequences. It is an unwanted consequence that might potentially generate major concerns that the activation of P450 activity shortens the duration of a drug's action by increasing the rate at which it is eliminated via metabolic processes. Furthermore, polyphenols have an effect on drug transport via interacting with drug transporters. One example of this is the P-glycoprotein, which is a member of the ABC transporter family. Both organic anion transporting polypeptides (OATPs) and organic cation transporters (OCTs) are other examples of this kind of membrane protein. It suggests the fact that there is a substantial possibility of harmful consequences coming from interactions between drugs and polyphenols⁸⁰⁻⁸⁵ (Table 3).

Possible Suppression of the intestinal microbiota alongside its effects

The particular polyphenol and bacterial species are having their different effects and their different mechanisms of their effect. The antibacterial activity of polyphenols is often ascribed to their interactions by metal, substrate, and protein deficiency, and the inhibition of damaging DNA or nucleic acid production. Reduction in the development of bacterial cell walls or interaction with them; cytoplasmic membrane permeability, fluidity, damage, and disruption; energy metabolism suppression; Preventing cell adhesion and biofilm. Digestion function may be impacted by polyphenols' inhibition of digestive enzymes and alteration of gut flora. The interactions between polyphenolic

food components and gastrointestinal bacteria are complex. Bacterial enzymes facilitate Polyphenols being released from the meal's component, thereby enhancing their bio accessibility and bioavailability. Furthermore, polyphenols are converted and degraded by bacteria, often by double bond reduction and hydrolysis processes. The gut microbiota has a diverse array of enzymes that facilitate activities beyond the capability of human enzymes, thereby enabling the transformation and utilization of all food components. The presence of polyphenols in foods for instance herbs, spices, fruits, and vegetables has been shown to be beneficial in suppressing the development of a variety of bacteria, equally Gram-positive and Gram-negative to be specific. Extracts of cloudberry, raspberry, and strawberry showed strong antibacterial action compared to *Salmonella enterica* ser. Typhimurium, *E. coli*, and *Lactobacillus rhamnosus*, including *L. rhamnosus* GG, especially at high concentrations. Strawberry extract has been proven to inhibit both *E. faecalis* and *Bifidobacterium lactis*. Myricetin suppressed the development of all lactic acid bacteria that were present in the human gastrointestinal tract flora; however, it did not inhibit the growth of *Salmonella* Typhimurium or *Lactobacillus plantarum* that came from beer. Specifically, the water-based extract of *Salvadora persica* L. demonstrated a dose-dependent inhibition of all tested bacteria. This was especially true for *Streptococcus mutans*, *S. faecalis*, *S. pyogenes*, *Staphylococcus aureus*, *Lactobacillus acidophilus*, *Pseudomonas aeruginosa*, and *Candida albicans*. On the other hand, the methanol extract of the same plant did not exhibit any activity towards *L. acidophilus* and *P. aeruginosa*. Polyphenol suppression of intestinal microbiota entails changes in their physiological function, such as the quantity of all bacterial metabolites including vitamins, amino acids, SCFA, antimicrobial peptides, and neurotransmitters that are vital to human health. In other words, polyphenols hinder the microbiota's ability to operate naturally. Furthermore, the involvement of microbiota in detoxification is disrupted, since these microbes degrade not only dietary items but also a variety of xenobiotics (such as pharmaceuticals), particularly molecules with branched chains or aromatic rings. Based on the findings of a number of research,

Table 3. Polyphenol and drug interactions- some important results

Drug (Medical Application)	Polyphenol/Type of Study	Impact on Drug Action Hypotheses and Affirmations	Ref.
Metformin is an anti-hyperglycemic medication specifically prescribed for the treatment of diabetes of the type 2 variety, especially in those who are overweight.	EGCG with green tea (also known as GT): a study	(i) GT reduced metformin absorption in a concentration-dependent manner, with IC ₅₀ standards of 1.4% (v/v) and 7.0% (v/v) for OCT1 and OCT2, correspondingly; (ii) GT's activity was higher for MATE1 than MATE2-K; (iii) Green tea. EGCG lowered metformin net uptake to 40% of non-EGCG levels, and reduced BSp and atorvastatin net uptake to 64% (not worth mentioning) and 69% (p < 0.05), correspondingly. (vi) GT	[86]
The benzodiazepine drug known as midazolam is used for the purposes of administering anaesthesia, providing sedation during procedures, treating acute agitation, and treating insomnia.	A pretreatment with either water or grapefruit juice was followed by the administration of midazolam/MDZ either intravenously (5 mg) or orally (15 mg) to a group of eight healthy male subjects.	After being administered intravenously, MDZ did not alter in terms of its pharmacokinetics or pharmacodynamic responses. When MDZ was pretreated with grapefruit juice, the peak plasma concentration (C _{max}) of the drug rose by 56%, the time it took to reach C _{max} (t _{max}) increased by 79%, and the area under the plasma concentration-time curve (AUC) increased by 52%. Bioavailability was enhanced from 24% ± 3% (water) to 35% ± 3% (grapefruit juice, p < 0.01), as a result of this. Additionally, there was a 105% increase in t _{max} and a 30% rise in area under the curve (AUC).	[87]
Digoxin is the earliest medicine used for the management of numerous heart problems, most often atrial coronary artery disease, fluttering of the atrium, as well as arrhythmia are all conditions that may occur.	In a human study, 16 healthy volunteers were given 0.5 mg of digoxin orally on Day 1, followed by 630 mg of green tea catechins/GTC and 0.5 mg of digoxin 1 hour later. The dosage of 630 mg of GTC was administered on its own from day 16 through day 28, and on day 29 the dosage of 630 mg of GTC plus 0.5 mg of digoxin was administered in the same manner as it did on day 15.	In contrast to taking digoxin alone, the concurrent treatment of digoxin and GTC considerably decreased digoxin systemic exposure: from time 0 to the final measured time, the geometric mean ratios (GMR) of the area under the concentration-time curve were 0.69 and 0.72, accordingly. The area under the curve (AUC) was the highest. Administering digoxin and GTC after GTC pretreatment (Day 29) lowered AUC last (GMR = 0.57) and C _{max} (GMR = 0.74), indicating that GTC coadministration lowers digoxin systemic exposure regardless of GTC pretreatment status.	[88]
Sildenafil (used for the treatment of male reproductive problems in addition to pulmonary arterial hypertension) used in conjunction with midazolam.	Green tea: in a clinical trial, ten people in good health took one tablet of sildenafil 50 mg and one tablet of midazolam 7.5 mg simultaneously. This was done either after drinking 250 mL of water or 250 mL of fresh extract made from 2 g of green tea. Additionally, following seven days of not being given any treatment, every participant tried the second option.	When GT was administered with sildenafil, the plasma concentrations rose (the area under the curve (AUC) increased from 484.2 ± 67.27 µg hr/L to 731.5 ± 111.01 µg hr/L, and the maximum concentration (C _{max}) increased from 318.9 ± 46.8 µg/L to 414.9 ± 67.0 µg/L). Additionally, the elimination rate constant and half-life of sildenafil were both lowered. Because patients who drink green tea are more likely to have adverse effects, it is possible that they may need lower doses of sildenafil while taking the medication.	[89]
Amlodipine (calcium channel inhibitor)	Over the course of ten days, rats were given amlodipine (30 mg/kg) orally at a dose of 1 mg/kg, regardless of whether they received EGCG treatment.	The pretreatment of EGCG Amlodipine was shown to increase the maximum concentration of C _{max} from 16.32 ± 2.57 to 21.44 ± 3.56 ng/ml (p < 0.05). Additionally, it decreased the maximum time of T _{max} from 5.98 ± 1.25 to 4.01 ± 1.02 hours. AUC _{0-t} was increased from 258.12 ± 76.25 to 383.34 ± 86.95 µg·h/L. Furthermore, the metabolic half-life was prolonged from 31.3 ± 5.6 to 52.6 µg·h/L.	[90]

certain polyphenols may enhance the growth of beneficial bacteria. Plant extracts or natural products that contain different polyphenols in their more organic forms (e.g., glycosides) are typically found to have a beneficial effect. Polyphenolic compounds that have been purified, particularly aglycones, which are not often found in food but are frequently found in dietary supplements, have negative impacts.⁹¹⁻⁹⁸

Blocking digestive enzymes is one of the effects of polyphenolic compounds

It is probable that condensed tannins and other natural polyphenols restrict the activity of digestive enzymes such as α -amylase, α -glycosidase, pepsin, trypsin, lipase, as well as chymotrypsin. It underscores the significance of dietary composition. They thus restrict the availability of nutrients and hinder digestion. Polyphenols have the capacity to attach to proteins, leading in the formation of soluble or insoluble complexes that have specific effects on the proteins' structure, function, solubility, hydrophobicity, thermal stability, isoelectric point, and susceptibility to digestive enzymes. Flavonoids form protein complexes by covalent bonding and nonspecific variables, including hydrogen bonding and hydrophobic effects. These changes may have an effect on food protein digestion and utilization, affecting organ function. In addition, polyphenols have the potential to affect the activity of digestive enzymes, which are proteins. These enzymes include lipases, proteases, and amylases. Changes in enzyme structure may degrade function and disrupt biochemical reactions or processes catalyzed by the enzyme. Hence, digestive enzymes are essential for human health, and any disturbance in their activity may impair athletic performance.

Polyphenols' inhibitory effect on digestive enzymes may harm those with enzyme deficiencies and dietary intolerances. The digestive disorders with the greatest prevalence are gluten sensitivity, coeliac disorder, lactose or complex carbohydrate intolerance, exocrine pancreatic insufficiency, cystic fibrosis, as well as pancreatic cancer. Glycosides like naringin, phloridzin, rutin, and arbutin reduced the active transport of glucose, while aglycones such as apigenin, myricetin, phloretin, and quercetin blocked

the increased absorption of glucose. Aglycones were shown to be effective in inhibiting glucose absorption. Non-glycosylated polyphenols found in food, such as (+)-catechin, (-)-epicatechin, (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epigallocatechin gallate (EGCG), exhibited steric hindrance and demonstrated their effectiveness against both transporters. These problems may develop with age or be inherited. Food intolerances or allergies may affect up to 20% of the general population, whereas 65% of IBS patients may suffer from them. Thus, digestive enzyme supplementation is becoming more popular among those suffering from lactose intolerance, coeliac disease, and cystic fibrosis. Food additives that inhibit certain enzymes must be identified for optimal diet planning and meal composition in such persons to prevent malnutrition.

The elderly are the last large group with reduced digestive enzyme function. Human studies found that bicarbonate and enzyme (lipase, chymotrypsin, and amylase) secretions were significantly lower in older individuals due to reduced secreted volume and enzyme concentrations⁹⁹⁻¹⁰⁵ (Table 4).

Summary

Particular polyphenols with possible adverse effects

Soy products include isoflavones, which are known to have estrogenic effects. While these effects may be advantageous to some women, they might cause hormonal imbalance in others. High soy isoflavone intake has been associated with thyroid issues and may impair fertility. Individuals with hormone-sensitive disorders should be cautious when taking large doses of soy isoflavones. Grapes, red wine, and additional plant sources comprise resveratrol, a stilbene. It has antioxidant, anti-inflammatory, and cardioprotective characteristics. Resveratrol is usually regarded as safe; however, it might induce gastrointestinal discomfort, nausea, and diarrhea in some people. High dosages of resveratrol may potentially interact with blood thinners, raising the risk of bleeding. Researchers recognize the antioxidant as well as anti-cancer activities of green tea catechins, particularly epigallocatechin gallate (EGCG). While green tea intake is typically

Table 4. Digestive enzymes repressed by polyphenols - some important results

Enzyme	Polyphenol	Assessment Methodology and Outcomes	Ref.
α -amylase	<ul style="list-style-type: none"> Tea polyphenols • Ellagittannins • Guaijaverin (1), Avicularin (2), Quercetin (3), Hyperin (4), Myricetin (5), apigenin (6), Kaempferol (7), as well as separated from the leaves of guava • Nine classifications of phenolic Tannic acid, chlorogenic acid, along with caffeic acid were identified, all worked well to stop amylase in YAP, with IC_{50} values of 0.30, 1.96, with 3.69 mg/ml, respectively. The sequence of the observed fixed polyphenols (YAP) are involved. • Raw components and heat-treated African Pear. 	<p>Tea polyphenols decreased enzyme activity and enhanced the affinity of swine duct α-amylase for starch.</p> <p>Ellagittannins suppress α-amylase activity.</p> <p>IC_{50} values of 3.5 mM, 5.2 mM, and 3.0 mM for compounds 1, 2, and 5 against sucrase, 4.8 mM, 5.6 mM, and 4.1 mM for compounds 1, 2, and 5 against maltase, and 4.8 mM and 5.3 mM for compounds 1 and 2, as well as 4.3 mM in relation to α-amylase, accordingly. Several hydroxyl groups that are related to the C-ring in the structure and the hydroxyl group at the A-ring's third position were crucial to the inhibitory action.</p>	[106] [107] [108]
α -amylase along with α -glucosidase	<ul style="list-style-type: none"> • Oolong varieties that are all manufactured from the same freshly selected leaves and have the same amount of tea polyphenols (TP). • Epicatechin-(4β-8)-epicatechin gallate (B2-32-O-gallate), epicatechin gallate(ECG), epicatechin (EC) 	<p>Actual three tea varieties markedly boosted α-amylase activities(0.34-27.14 mg/ml), with green tea having the most pronounced impact. However, higher TP concentrations reduced its activity marginally in an ineffective manner.</p>	[111]
Maltase & sucrase and α -glucosidases	<ul style="list-style-type: none"> • Epicatechin-(4β-8)-epicatechin gallate (B2-30-O-gallate), epicatechin gallate(ECG), epicatechin (EC) 	<p>The IC_{50} values for B2-30-O-gallate were $1.73 \pm 1.37 \mu\text{m}$ and $6.91 \pm 3.41 \mu\text{m}$ for maltase, $3.64 \pm 2.99 \mu\text{m}$ for EC, and $18.27 \pm 3.99 \mu\text{m}$ for maltase, as well as $18.91 \pm 3.66 \mu\text{m}$ for sucrase.</p>	[112]
Pepsin	<ul style="list-style-type: none"> • Ten flavonoids. 	<p>It has been shown by spectroscopic and molecular docking techniques that all flavonoids have the potential to attached to pepsin, resulting in the formation of flavonoid-pepsin complexes. For the most part, electrostatic forces and hydrophobic contacts at a single binding site are responsible for this spontaneous contact, which ultimately results in a decrease in enzyme activity.</p>	[113]
Trypsin	<ul style="list-style-type: none"> • Quercetin (Q), luteolin (LUT), Hesperidin (HES), rutin (RUT) and catechin (CAT). 	<p>Methods such as circular dichroism, molecular docking of flavonoids-trypsin complexes, and UV-visible, intrinsic, and extrinsic fluorescence spectroscopies were used to illustrate the phenomenon of static quenching respectively. LUT was shown to be the most potent trypsin inhibitor, with an IC_{50} value of $45.20 \pm 1.00 \mu\text{M}$. This was due to the fact that hydrophobic interactions between flavonoids and trypsin were the predominant feature.</p>	[114]

harmless, excessive amounts of green tea extracts or supplements may cause liver damage in some people. When taking in a lot of green tea catechins, it is important to keep an eye on how your liver is working. A flavonoid called quercetin may be found in a variety of fruits and vegetables. It has been recognized as being an antioxidant as well as an anti-inflammatory. Although large dosages of quercetin might cause headaches and gastrointestinal problems, it is generally considered safe. It may also interfere with several medicines, including antibiotics and chemotherapy therapies.¹¹⁵⁻¹¹⁹

Composition of food, bioavailability, and interactions with other substances

Whenever polyphenols are consumed, the dietary composition in which they are contained may influence their bioavailability and biological activity. Polyphenols may interact through additional nutritional constituents for example proteins, carbohydrates, as well as lipids, increasing or decreasing their absorption. Bacteria in the stomach have a significant influence on polyphenol metabolism and bioavailability. Polyphenols may interact with a broad spectrum of substances, together with medications, minerals, as well as other compounds that included in the meal plan. These interactions possess the capacity to alter the effects of both polyphenols and other medicines. Before starting to utilize polyphenol supplements, you should be aware of the various potential interactions and seek the counsel of a trained medical practitioner, especially if you are currently on any medications.^{116,119-122}

CONCLUSION

Global efforts are undertaken to reduce malnutrition by promoting optimum growth and health outcomes. Food is unquestionably an important component of long-term, optimal health. Natural polyphenols provide several health advantages and are an important component of plant-based meals. They may be considered non-essential nutrients. Among the foods that contain polyphenols include herbs, spices, fruits, and vegetables. Polyphenols possess biological activity, together with antioxidant, anti-inflammatory, and anti-cancer characteristics. Polyphenols are

a valuable source of anti-infective compounds that may help cure antibiotic-resistant infections in humans by killing germs and suppressing cell growth.

In addition, many polyphenols each have their own set of negative consequences. Some of the nutrients interact with many other substances and undergo chemical changes during cooking and storage, reducing their stability and bioavailability. Food combinations, cooking methods, and dietary habits affect health outcomes, including ageing and life expectancy, although little is understood. The enzymes α -amylase, α -glycosidase, pepsin, trypsin, lipase, and chymotrypsin are among the digestive enzymes that may be hindered by natural polyphenols such condensed tannins. This highlights food composition. They reduce digestion and nutritional availability. It also implies that polyphenol-drug interactions may cause damage. The healthcare professional and patient must be informed of any established relationships among often used medication and diet or herbal treatments. All cultures have food-related folk knowledge that needs scientific validation. Our existing nutritional research methodologies look unsuitable for population-level food and dietary study and should be revised. Our scientific knowledge of the nutrients needed for survival and good health, the foods that can provide those nutrients, and the best eating and dietary habits for long-term, healthy survival is remarkable. More scientific data and knowledge of nutrition, food, and diet's biochemical, physiological, and cultural aspects are needed to make educated recommendations and execute them internationally while considering everyone's social, cultural, and environmental demands. It needs more research into the mechanisms of action of polyphenolic metabolites or polyphenol delivery methods that maximise bioavailability while minimising health damage. In conclusion, more study on dietary polyphenols such as resveratrol, EGCG, quercetin, apigenin, and curcumin is needed to establish their potential as health supplements that are both affordable and easily accessible.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

SKM, NO, RJ, HAA, ADA, MAA and MRA conceptualized the study. SKM, NO, RJ, HAA, ADA and MAA collected resources. NO, RJ, HAA, ADA and MRA supervised the study. SKM wrote the manuscript. HI, MAA and MRA reviewed and edited the manuscript. All authors read and approved the final manuscript for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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