Al-Kitab Journal for Pure Sciences (2025); 9(2):104-127.
https://doi.org/10.32441/kjps.09.02.p7

Al-Kitab Journal for Pure Sciences
ISSN: 2617-1260 (print), 2617-8141(online)

https://isnra.net/index.php/kjps

Polyphenols of Mulberry White (*Morus alba L.)* Leaves as a Source of Functional Food: A Review

Hagar F. Forsan[1]*, Menatalla R. Fayed[2], Noureldin M. Farahat[3], Ezzeldeen M. Alswerky[4], Walaa M. Gabr[5], Asmaa E. Abd El-Hak[6], Mohamed A. Fouda[7], Mennat-Allah Safwat[8]

[1]*Animal Production Research Institute (APRI), Agricultural Research Center (ARC), Dokki, Giza, Egypt, [2] Faculty of Pharmacy, Sinai University, North Sinai, Egypt, [3] Faculty of Pharmacy, Alexandria University, Alexandria, Egypt, [4] Faculty of Science, Islamic University of Gaza, Gaza, Palestine, [5]Faculty of Science, Mansoura University, Dakahlia, Egypt, [6] Faculty of Agriculture, Ain Shams University, Cairo, Egypt, [7] Faculty of Agriculture, Tanta University, Gharbia, Egypt, [8] Faculty of Pharmacy, Alazhar University, Cairo, Egypt.

*Corresponding Author: hagarfathy@pg.cu.edu.eg

Citation: Forsan HF, Fayed MR, Farahat NM, Gabr WM, Alswerky EM, Abd El-Hak AE, Fouda MA, Safwat MA. Polyphenols of Mulberry White (Morus alba L.) Leaves as a Source of Functional Food: A Review. Al-Kitab J. Pure Sci. [Internet]. 2025 Apr. 30; 9(2):104-128. DOI: https://doi.org/10.32441/kjps.09.02.p7.

Keywords: Mulberry Leaves; Phenolic Compounds; Extraction; Metabolism; Health Benefits.

Article History

Received 05 Sep. 2024
Accepted 27 Oct. 2024
Available online 30 Apr. 2025

Abstract:

Mulberry is a plant that grows in temperate to subtropical climates. Mulberry leaves are economically feasible due to their historical importance in sericulture, so their production increases yearly, but the large output leads to a large percentage of residues. As a result, it was largely accumulated, creating controversial consequences, rather than being reintegrated into the manufacturing process for a new function. However, this residue in mulberry leaves naturally contains high levels of bioactive compounds, especially polyphenols. Mulberry leaves have a vital pharmaceutical potential role as antibacterial and antioxidant. Mulberry leaves have many health benefits, such as anticancer, antiviral, and anti-obesity etc. However, many extraction methods can benefit different uses as food innovation, leading to added-value products. So, the current review article provides a comprehensive discussion concerning extraction methods, metabolism, health effects such as Anticancer, Antidiabetic**,** Anti-obesity, Activity of anticonvulsant, Antiatherosclerosis, and SARS-CoV-2 inhibition, and various uses in the food industry.

Keywords: Mulberry Leaves; Phenolic Compounds; Extraction; Metabolism; Health Benefits.

بولي فينولات أوراق التوت (*Morus alba L.*) كمصدر للغذاء الوظيفي: مقال مرجعي

هاجر فتحي فرسان[١]، منة الله رضا فايد[٢]، نورالدين محمد فرحات[٣]، عزالدين محمد السويركى[٤] ، ولاء محمد جبر[٥] ، اسماء عماد عبدالحق[٦] ، محمد أشرف فودة[٧] ، منه الله صفوت[٨]

[١]معهد بحوث الإنتاج الحيواني، مركز البحوث الزراعية ،الدقي، الجيزة، مصر/ [٢] كلية الصيدلة، جامعة سيناء، شمال سيناء، مصر/ [٣]كلية الصيدلة، جامعة الإسكندرية، الإسكندرية، مصر/ [٤] كلية العلوم، الجامعة الإسلامية، غزة، فلسطين/ [٥] كلية العلوم، جامعة المنصورة، الدقهلية، مصر/ [٦] كلية الزراعة، جامعة عين شمس، القاهرة، مصر/ [٧] كلية الزراعة، جامعة طنطا، الغربية، مصر/ [٨] كلية الصيدلة، جامعة الأزهر، القاهرة، مصر

hagarfathy@pg.cu.edu.eg, su.14011384@su.edu.eg, D06201915411@alexu.edu.eg, eswerky@students.iugaza.edu.ps, alaa300@std.mans.edu.eg, asmaa_emad@agr.asu.edu.eg, mohammed30935346@agr.tanta.edu.eg, Mennat-allahAbdelsalam5928@azhar.edu.eg

الملخص:

ينمو نبات التوت بكثافة في المناطق ذات المناخ المعتدل وشبه الاستوائي. وتكتسب أوراق التوت أهمية اقتصادية نظرًا لدورها التاريخي في تربية دودة القز، مما أدى إلى زيادة إنتاج نبات التوت سنويًا. إن الزيادة الكبيرة في الإنتاج تتسبب في تراكم كميات كبيرة من المخلفات. هذه المخلفات تراكمت بمرور الوقت بشكل كبير، مما أوجد تحديات بيئية واقتصادية. وُجد أن مخلفات أوراق التوت تحتوي على مستويات مرتفعة من المركبات النشطة بيولوجيًا، وخاصة البوليفينولات. تلعب أوراق التوت دورًا مهمًا في المجال الصيدلاني، حيث تتمتع بخصائص مضادة للأكسدة والبكتيريا. كما أن لها فوائد صحية متعددة، منها الوقاية من الإصابة بمرض السرطان، والوقاية من السمنة، كما أنها مضادة للفيروسات وغيرها. وُجد أن هناك العديد من طرق الاستخلاص التي يمكن الاستفادة منها في مختلف المجالات، بما في ذلك الابتكار الغذائي، مما يساهم في إنتاج منتجات ذات قيمة مضافة. يستعرض هذا المقال بشكل شامل طرق الاستخلاص، والتمثيل الغذائي، والفوائد الصحية لأوراق التوت، مثل مكافحة السرطان، ومكافحة السكري، ومكافحة السمنة، والوقاية من التشنجات، والحد من تصلب الشرايين، وتثبيط فيروس SARS-CoV-2 ، فضلاً عن الاستخدامات المتنوعة في الصناعة الغذائية.

الكلمات المفتاحية: أوراق التوت، المركبات الفينولية، الاستخلاص، التمثيل الغذائي، الفوائد الصحية.

1. Introduction:

The Morus genus (Moraceae) has about 19 members, most are in the northern temperate zone. White, black, and red mulberries are the highest prevalent types. *Morus alba* is the most common species grown in South Europe, Turkey, Southwest Asia, and Central Asia. This plant's various morphological components (fruits, leaves, roots, and stems) have been used for various purposes. The primary contents are fruits and leaves **[1]**. In a circular and sustainable bioeconomy, organic agricultural wastes like mulberry leaves are utilized as extraction material, and recovery chemicals are reinserted into the production chain. scientists use different recovery procedures to acquire bioactive compounds. Mulberry leaves have therapeutic benefits **[2]**. Mulberry leaves are also used as an anti-hyperglycemic supplement by people with diabetes in

Japan and Korea, high blood pressure, alcohol hangovers, throat infections, irritations, and infections. Mulberry tea usage has risen in recent decades due to its hypoglycemic, depressive, antioxidant, and hepatoprotective properties [3]. Mulberry leaves are approved as a great source due to the high concentration of protein, carbohydrates, vitamins, microelements, and dietary fiber. It is also high in flavonoids, alkaloids, phenolic acids, and gamma-aminobutyric acid [4]. Chlorophyll, the green pigment found in mulberry leaves, plays a crucial role in photosynthesis, allowing plants to convert light energy into chemical energy. In addition to its primary role in plants, chlorophyll in mulberry leaves offers several health benefits when consumed by humans [5]. Anti-HIV, antioxidative, hypotensive, cytotoxic, hypoglycemia, hepatoprotective, neuroprotective, and anti-inflammatory activities are all present in these bioactive molecules. They've also been used to treat antibacterial and anti-obesity conditions. Plants have since been exploited in phytotherapeutic activities and other industrial uses as a source of pharmacologically bioactive compounds, mainly for medications that treat various ailments. Various plants require the ability to scavenge free radicals for the food business [6]. Caffeic acid, kaempferol-3-O-(6-malonyl)–glucoside, quercetin-3-O-(6-malonyl)–glucoside, caffeoylquinic acids, and quercetin-3-O-glucoside are among phenolic acids and flavonoids found in Mulberry leaves [7], Figure 1 [8]. This review aims to thoroughly explain extraction techniques, metabolism, anticancer, antidiabetic, anti-obesity, anticonvulsant, anti-atherosclerosis, and SARS-CoV-2 inhibitory health effects, as well as diverse applications in the food sector.

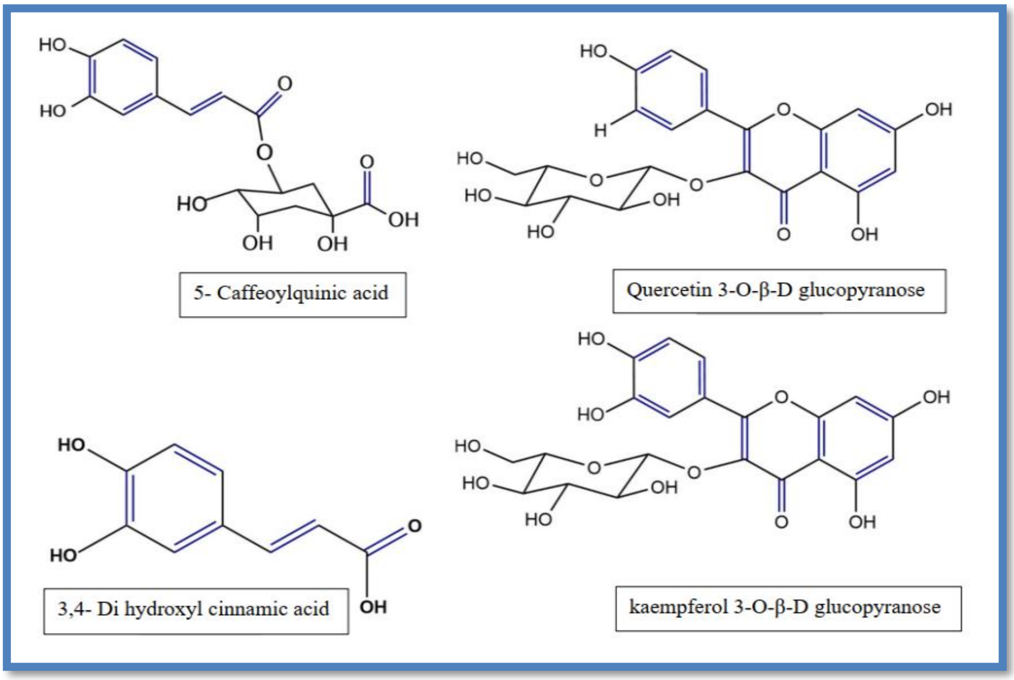

Figure 1: Phenolic acids identified from Mulberry leaves [7, 8].

2. Extraction methods

2.1 Low-pressure liquid chromatography (LPLC)

2.1.1 Mulberry leaf sample preparation: Researchers used dried plant material from mulberry leaves. The materials were sieved after being reduced to a fine powder to find the optimal particle size for green tea catechin extraction. The powder was maintained in airtight jars and kept at a temperature of 4°C [9].

2.1.2 Extraction: The following steps were used to extract lipids from Mulberry leaves in the first instance. n-hexane (250 mL) was used to homogenize dried Mulberry leaves (10 g), centrifuged at 4390 g for 5 minutes after being homogenized for 10 minutes in an ice bath. In the following step, the residue was added after removing the supernatant to 250 mL precooled alcohol/water combination (8:2, by volume) to create the final product. Separate extractions were performed on the mixture using a homogenizer at 5000 rpm for 5 minutes and a centrifuge at 4390 g for 5 minutes. Two supernatants were mixed and dehydrated in a RE-52AA rotary evaporator at 50°C. Each extraction's dry residue was dissolved in an 8/2 methanol/water solution. The solution was filtered through a filter membrane (0.22 m; 25 mm Luer syringe filter) and stored at 80°C till analysis. Each extraction took two steps. The residue was preserved for upcoming use. Solvent for extraction was discovered in an 8:2 binary mixture of water, organic solvents (e.g., acetone), and other organic solvents. Diamonsil C18 reversed-phase column with methanol as solvent (250 nm 4.6mm, 5 m, Dikma, Beijing). Mobile phases A and B were 0.01 % phosphoric acid (A) and 0.01 % acetonitrile (B), with gradient elution as follows: 18-23 % B; 29-36 % B; 36-43; 43-50 % B. The column was also set at 30°C with 0.9 mL/min flow [10, 11].

3. Quantitative phenolic analysis of black mulberry leaf extracts

Low-pressure liquid chromatography with SPD-M10AVP diode array detector (200–550 nm), CTO-10 column oven, LC-10 ADP pump, Reodayn Valve type 7725i manual sample injection, and CBM-10A communications bus module. The following materials were dissolved in 50 mL MeOH in a volumetric flask 50 mL: (80:20; v/v) rutin trihydrate, hydroxycinnamic acid, color Serial dilutions in a MeOH: H2O (80:20; vol/vol) solvent phase yielded concentrations of 10–500 g/mL. The Low-pressure liquid chromatography was used to test seven standard solution concentrations (10–500 g/mL). In this case, an Intersil ODS-3 reverse phase column (25 cm 4.6mm, 5 m particle size) was used. It was done at 1 mL/min using 20 L of standards and extracts. All solutions were filtered using a 0.45 m syringe filter before Low-pressure liquid chromatography analysis. The mobile phase was acetic acid (vol/vol) and

MeOH (solvent A) (solvent B). Conditions of gradient were nominal values: 0 (100), 3, 95 (95), 18, 80 (25), 75 (75), 60 (60), 55 [12], 65 (40), and 100 (100). During the acquisition of the chromatograms, the UV spectra of each chemical were obtained using a diode array detector. For gallic acid monohydrate, (—) –gallocatechin, vanillic acid, ellagic acid, trans-ferulic acid, hydroxycinnamic acid, kaempferol, (+)–catechin, and (—) –epicatechin, the maximum wavelengths were 280 nm for gallic acid monohydrate, (—) –gallocatechin, vanillic acid, ellagic acid, trans-ferulic acid [13].

4. High-performance liquid chromatography

4.1 Collection and preparation of samples of Mulberry leaves: In High-Performance Liquid Chromatography (HPLC) analysis, the collection and preparation of samples of mulberry leaf extracts is a critical step to ensure accurate and reliable results. The process typically begins with the collection of fresh or dried mulberry leaves, which are then thoroughly cleaned to remove any dirt or contaminants. The leaves are air-dried or oven-dried and ground into a fine powder to increase the surface area for extraction. In this process, heating the Mulberry leaves to 55°C and drying it for 6–8 hours is a typical approach to remove moisture, ensuring the stability of bioactive compounds. Pulverizing the dried Mulberry leaves into a powder increases its surface area, facilitating more efficient extraction of polyphenols or other compounds during further analysis. Storing the powder at 2°C until use helps preserve the integrity of these bioactive compounds, preventing degradation from environmental factors like light or heat. This method ensures that the Mulberry leaves remains in good condition for subsequent studies or extractions

4.2 Free phenolic extraction: A RE-52AA rotary evaporator was used to dry two supernatants at 50°C. The "two supernatants" refer to the liquid fractions obtained from two distinct extraction steps that utilize different solvents or methods. The first supernatant is derived from an initial extraction using a non-polar solvent, such as n-hexane, which is typically employed to extract lipid or non-polar compounds. After homogenizing the dried mulberry leaves with n-hexane, centrifugation separates the mixture, yielding a supernatant rich in lipid-soluble compounds. The second supernatant comes from a subsequent extraction using a different solvent system, often a mixture of alcohol and water (for instance, ethanol and water in an 8:2 ratio), aimed at isolating free phenolic compounds that are more soluble in polar solvents. Following this extraction, the mixture undergoes centrifugation again, resulting in a supernatant containing the desired free phenolics. Both supernatants are then dried separately using a rotary evaporator at 50°C, concentrating their respective bioactive compounds before further analysis or processing. This method effectively ensures the extraction of both lipid-soluble and phenolic compounds from the mulberry leaves.

Or make a methanol and water solution to dissolve the dry extraction residue. The solution was filtered using 0.22 m membrane filters and preserved till analysis at 80°C. Each extraction took two steps. The remnants were preserved for future use. Various organic solvents, such as ethanol, were used to create 8:2 binary mixtures of organic solvents and water to determine the best extraction solvent **[14]**. The following steps were used to extract lipids from the Mulberry leaves in the first instance. n-hexane (250 mL) was used to homogenize dried mulberry leaves (10 g), which were centrifuged at 4390 g for 5 minutes after being homogenized for 10 minutes in an ice bath **[15]**. The final product was made by removing the supernatant and mixing it with 250 mL precooled alcohol and water (8:2, by volume). The mixture was homogenized (5000 rpm, 5 minutes) and centrifuged separately (4390 g, 5 minutes).

4.3 Bound phenolic extraction: After phenolics were extracted freely, Mulberry leaves residues were used to hydrolyze bound phenolics in acetone **[15]**. The substance was subjected to both alkaline and acid hydrolyzed, and alkaline hydrolysis was performed **[16]**. The residue was hydrolyzed under nitrogen gas flow for 1.5 hours with 2 M NaOH (100 mL). HCl (6 M) was added six times to obtain pH 2. This extract was vaporized to dryness at 45°C. The dried Mulberry leaves extracts were reconstituted in methanol 80%, filtered, and kept at –80°C. Acid hydrolysis was performed using the Dongxiao method. This was followed by 1.5 hours at 85°C in a mix of methanol and concentrated sulfuric acid (90:10) with nitrogen gas flow. The mix was neutralized to pH 2 using NaOH (10 M) for six extractions. This extract evaporated to dryness at 45°C.

The Dongxiao technique was used to achieve acid hydrolysis. After that, 1.5 hours at 85°C with nitrogen gas flow were spent in a combination of methanol and concentrated sulfuric acid (90:10). The mix was neutralized to pH 2 using NaOH for six extractions (10 M). At 45°C, this extract evaporated to dryness. Dietary supplements should not be taken with dried extracts. Dried extracts should be approached with caution when it comes to their use in dietary supplements for several important reasons. Firstly, these extracts can exhibit potency variability due to differences in raw material quality, extraction methods, and processing conditions, leading to inconsistent concentrations of active compounds and making it challenging to determine effective dosages for health benefits. Additionally, the drying process can cause the degradation or loss of sensitive bioactive compounds, as exposure to heat, light, and oxygen may break down certain vitamins, antioxidants, and phytochemicals, thereby diminishing their efficacy in the final product. Furthermore, improperly purified dried extracts may harbor contaminants like pesticides, heavy metals, or microbial toxins, posing significant health risks, particularly since dietary supplements are often not adequately regulated. The lack of standardization in many dried extracts complicates matters further, as consumers cannot be assured of specific active ingredient levels, making it difficult to understand their health impacts. Moreover, the potent biological effects of dried extracts can lead to interactions with medications, potentially causing adverse effects or diminishing the effectiveness of prescribed treatments, especially for those with pre-existing health conditions or multiple prescriptions. Finally, while some dried extracts show promise in preliminary studies, there is often limited clinical evidence supporting their safety and efficacy, which hinders confident recommendations for their use. For these reasons, consumers must consult healthcare professionals before using dietary supplements containing dried extracts, ensuring informed choices tailored to their specific health needs and conditions.

4.4 Total Polyphenol Content (TPC) determination

4.4.1 Extraction of Mulberry leaves: To create Mulberry leaves extract, approximately 200 mg of Mulberry leaves powder was properly weighed and combined with 20 mL of a solution containing ethanol and deionized water (70:30, vol/vol). The mixture was put in an ultrasonic cleaning bath (KQ-2200DB, 100W, Kunshan, China) and removed twice for a total of 20 minutes at 30 °C each time. The extracts were filtered via filter paper to remove any impurities. Last but not least, the filtrate was diluted with 70 % (vol/vol) ethanol in water to get 50 mL **[17]**.

4.4.2 Determination of Total Polyphenol Content (TPC): Using a slightly modified Folin-Ciocalteu technique, total polyphenols in Mulberry leaves were shown to be substantial. 40 ul of Folin-Ciocalteu reagent (2N) was mixed with the samples. A blank sample of 40 ml ethanol 70% ethanol was combined with diluted Folin-Ciocalteu solution and used for instrument auto zeros. The mixture was neutralized for 1–2 hours at room temperature before adding 1.2 mL of 7.5 percent sodium carbonate solution to test for pollutants. The absorbance was measured at 765 nm. The total polyphenol concentrations were expressed as gallic acid equivalents ($y=0.6812x+0.0314$, $R2=0.9975$, calibration range 0.0078125 mg/mL to 0.5 mg/mL, and absorbance 0.0308 and 0.3678, respectively). Total polyphenols as gallic acid equivalents **[17]**.

The Total Polyphenol Content of mulberry juice can be determined using the Folin-Ciocalteu colorimetric method, which is a widely used technique for quantifying polyphenols. In this process, the Folin-Ciocalteu reagent, a mixture of phosphomolybdate and phosphotungstate, reacts with polyphenols present in the juice. When polyphenols reduce these complexes, a blue color develops, with the intensity of the color directly proportional to the polyphenol concentration. The absorbance of the solution is then measured spectrophotometrically, typically at a wavelength of around 765 nm. The results are compared to a standard, often gallic acid, and expressed as gallic acid equivalents **[18]** to quantify the total polyphenol content in the mulberry juice **[19]**.

5. HPLC determination of phenolic

The HPLC setup for analyzing phenolic compounds involves several critical components for effective separation and quantification. Column Specification: An ADME column (5 µm, 250 × 4.6 mm) is employed, which is suitable for separating a wide variety of phenolic compounds based on their polarity and size. Mobile Phase Composition: The method utilizes a mobile phase comprising phosphoric acid and water (0.2:100) as one solvent, alongside acetonitrile as the second solvent, enhancing the solubility of phenolic compounds in an acidic environment for improved separation. Gradient Program: A gradient elution method is employed with varying percentages of acetonitrile (solvent B) over specific intervals, which facilitates the optimized separation of phenolic compounds. The program involves starting at a lower percentage, gradually increasing to 30%, then 40%, decreasing to 20%, increasing again to 35%, and reaching 71% before decreasing to 76%. This approach allows for the elution of different phenolic compounds at distinct times, thereby enhancing resolution. Flow Rate and Temperature: A standard flow rate of 1 mL/min is maintained, striking a balance between resolution and analysis time, while the column temperature is kept at 25°C to ensure consistent performance of the stationary phase. Detection Wavelengths: Chromatograms are acquired at 280 nm and 350 nm, which are optimal wavelengths for detecting many phenolic compounds due to their strong UV absorbance at these points. Overall, this HPLC method accurately detects and quantifies phenolic compounds, making it suitable for analyzing samples such as mulberry leaves and other plant extracts **[20, 21]**.

6. Health-promising effects of polyphenols in Mulberry leaves

Polyphenols found in mulberry leaves offer a variety of health benefits. These benefits range from managing blood sugar levels and lipid profiles to safeguarding organs from oxidative stress and inflammation. Their physiological effects, which include antioxidant, anti-inflammatory, and antimicrobial properties, position them as strong candidates for both disease prevention and treatment. Besides, they play a role in protecting essential organs such as the heart, brain, liver, and skin from damage. Such health advantages emphasize the considerable potential of polyphenols in the fields of pharmaceutical development and dietary supplements aimed at enhancing overall health and longevity.

6.1 Neurocognitive effects: Recent studies have also suggested that some gut microbiota (gm)-derived phenolic metabolites may have neurocognitive effects, such as improving memory and cognitive function **[22-24]**. Phenolic metabolites can have direct neurocognitive impacts by passing through the blood-brain barrier (BBB) and boosting levels of neurotransmitters like dopamine, which are examples of indirect brain effects. The primary purpose of this crucial physiological barrier is to keep dangerous compounds out of the brain, but it can also keep xenobiotics like polyphenols out. Thus, the effects of phenolic compounds (PCs) on the central nervous system (CNS) largely depend on their capacity to pass through the BBB **[25]**. The production of phenolic metabolites by the microbiota has been well-studied, but their permeability across the blood-brain barrier has just recently come to light **[26]**.

6.2 Anticancer: Mulberry leaves, derived from Morus species, contain a high concentration of polyphenols, which are natural substances with various biological activities, including properties that may help fight cancer. The main types of polyphenols found in mulberry leaves are flavonoids (like quercetin, rutin, and isoquercitrin), phenolic acids (including caffeic acid and gallic acid), and stilbenes. These compounds have been thoroughly researched for their potential health advantages, such as antioxidant, anti-inflammatory, and anticancer effects. Polyphenols in mulberry leaves function as strong antioxidants, neutralizing harmful free radicals that can damage DNA and contribute to cancer development by minimizing oxidative stress and shielding cells from mutations that may lead to cancer. They also exhibit anti-inflammatory properties, as compounds like quercetin and rutin have been shown to block pro-inflammatory cytokines and enzymes (such as COX-2), which play a role in the progression of cancer. Also, polyphenols encourage apoptosis (programmed cell death) in cancerous cells through pathways such as caspase activation, which helps eliminate compromised or cancerous cells while preserving healthy ones. What's more, specific polyphenols, such as quercetin, hinder the growth and spread of cancer cell lines (including breast, lung, and liver) by obstructing essential signaling pathways related to cell cycle progression, such as the PI3K/Akt and MAPK pathways. They also impede angiogenesis, the process of forming new blood vessels necessary for tumor growth, by downregulating the expression of vascular endothelial growth factor (VEGF). Flavonoids like rutin inhibit the migration and invasion of cancer cells, thereby decreasing metastasis by interfering with metalloproteinases (MMPs) that break down the extracellular matrix. Research has shown that polyphenols from mulberry leaves can inhibit the proliferation of liver cancer cells, induce apoptosis through the mitochondrial pathway, and exhibit cytotoxicity against breast cancer cells by modulating estrogen receptor signaling. In models of colon cancer, these polyphenols suppress tumor growth and lower carcinogenesis risk by influencing GM and reducing inflammation. Overall, the polyphenols in mulberry leaves demonstrate major anticancer potential by fighting oxidative stress, inflammation, tumor growth, and metastasis. Although these findings indicate that mulberry leaves may be an effective supplement for cancer prevention and treatment, further clinical trials in humans are essential to validate these outcomes [27].

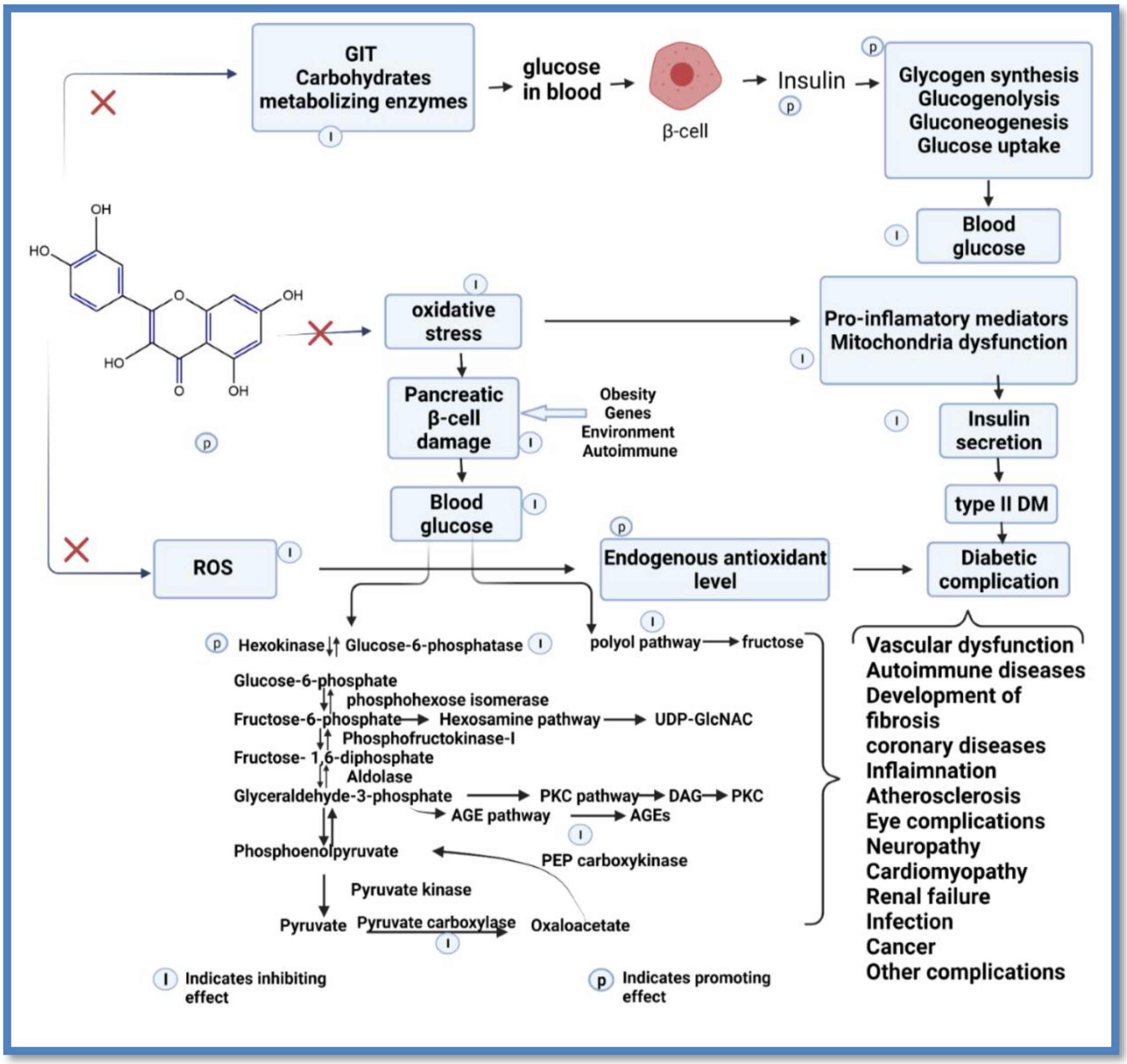

Figure 2: Antidiabetic mechanisms of dietary polyphenols. Adapted with permission from Ref. [28] Copyright 2024, Wiley

6.3 Antidiabetic: Consumption of dietary polyphenols reduces diabetes risk problems such as vascular dysfunction and failure for renal, protects pancreatic islet cells, reduces apoptosis, increases cell proliferation, decreases oxidative stress, activates insulin signaling, and stimulates insulin secretion are some of the insulin-dependent and insulin-independent approaches that have been studied in vivo and in vitro as shown in **Figure 2** and **Figure 3 [28]**. High blood glucose impacts small-molecule medications' absorption, distribution, biotransformation, and excretion. Medication bioavailability and polyphenols in food vary depending on daily dosages, component complexity, and dietary interaction. Dietary polyphenols are little absorbed and quickly excreted. Only 5–10% of polyphenols are absorbed, while 90% of polyphenols digested are excreted in the colon. The majority of clinical drugs are properly absorbed and delivered. Carbohydrate, protein, and lipid metabolism are all affected by high blood sugar. The mechanisms that control these biochemical processes often also engage in phytochemical biotransformation. Thus, hyperglycemia impacts the bioavailability of dietary polyphenols. For example, diabetic mice show higher Cmax and AUC of mangiferin, baicalin, wogonoside, and oroxyloside **[29]**. Phlorizin bioavailability increased in rats with type 2 diabetes **[30]**. Diabetic rats absorbed more cynaroside and other antioxidants than non-diabetic rats. The Zucker diabetic fatty rat demonstrated lower Cmax values for catechin, epicatechin, quercetin, and resveratrol conjugated metabolites than the Zucker diabetic fatty rat **[31]**. methylation flavan-3-ol, resveratrol, and quercetin bioavailability metabolite considerably reduced in Zucker fatty diabetic rats **[31]**. Research on hyperglycemia-induced alterations in phytochemical bioavailability has stalled. Finding out how hyperglycemia affects dietary polyphenol bioavailability will allow us to use these polyphenols better and enhance clinical outcomes, as illustrated in **Figure 4**.

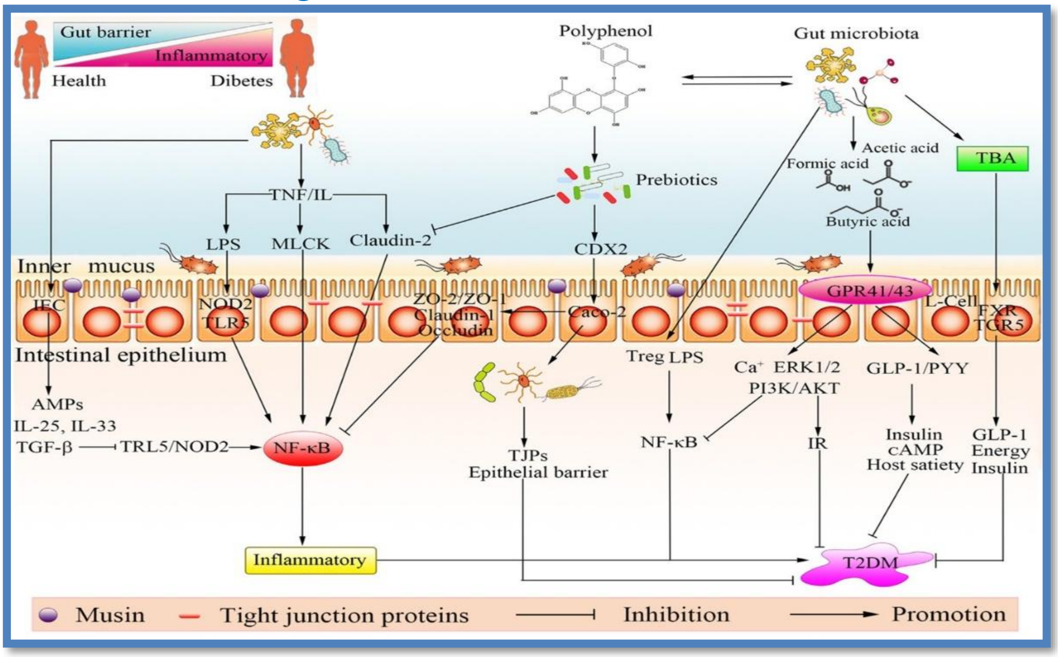

Figure 3: Polyphenols and gut microbiota diabetes effects. Adapted with permission from Ref. [28] Copyright 2024, Wiley.

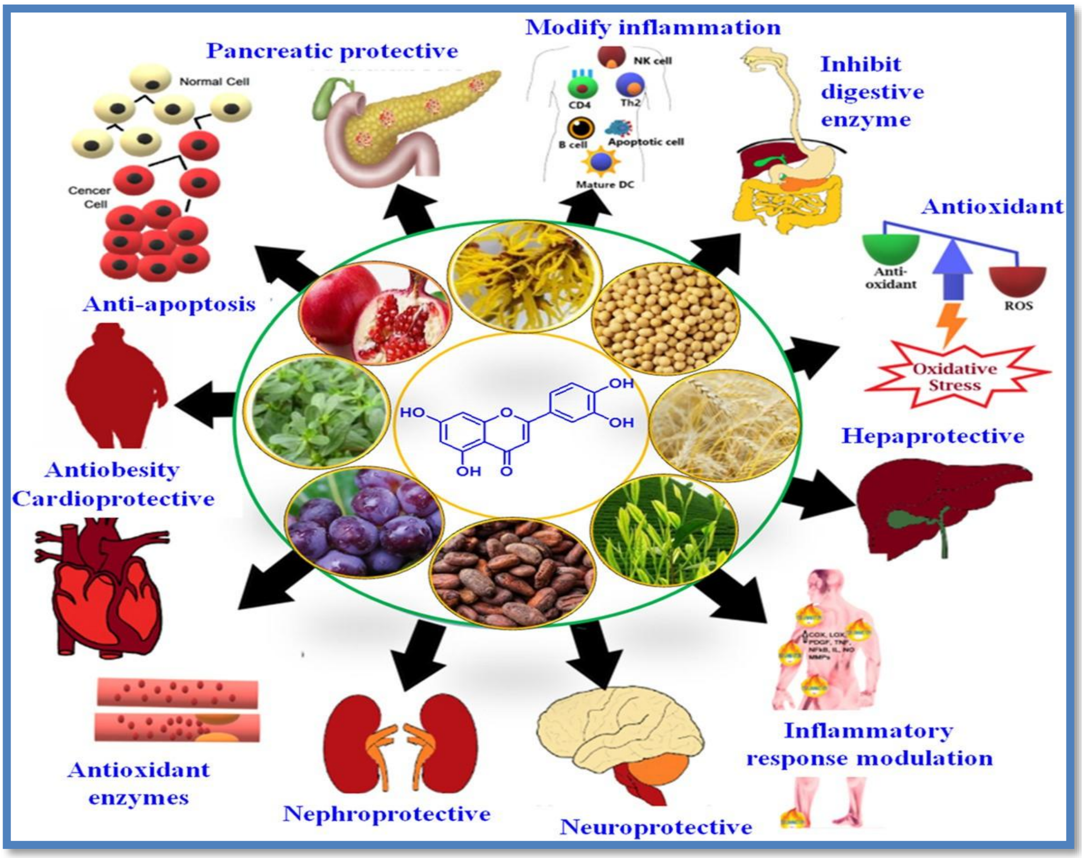

Figure 4: Dietary polyphenols Antidiabetic effects. Adapted with permission from Ref. [28] Copyright 2024, Wiley.

6.4 Anti-obesity: Mulberry leaves may help in managing obesity thanks to their high levels of polyphenols, particularly flavonoids like quercetin and rutin, which play a role in several mechanisms. They assist in regulating blood glucose and insulin sensitivity by inhibiting carbohydrate-digesting enzymes, such as alpha-glucosidase and alpha-amylase, which slow sugar absorption and prevent blood sugar spikes. Mulberry leaf extracts also improve lipid metabolism, encouraging the breakdown of fats and blocking the formation of new fat cells (adipogenesis), while also affecting genes related to fat metabolism, thereby aiding in weight loss. Besides, their anti-inflammatory and antioxidant properties may help diminish chronic inflammation and oxidative stress, which are often associated with complications related to obesity, such as insulin resistance and metabolic syndrome. By inhibiting pancreatic lipase, these extracts can reduce fat absorption, which further supports weight loss. In addition, some studies indicate that mulberry leaves may influence appetite by affecting hunger-related hormones, although further research is necessary to verify this effect in humans. In summary, mulberry leaves present promising advantages for managing obesity through the enhancement of glucose metabolism, reduction of fat accumulation, and improvement of metabolic health **[32]**.

6.5 Activity of anticonvulsant: Mulberry leaves are rich in polyphenols, including flavonoids and phenolic acids, which have demonstrated potential anticonvulsant properties in various studies. These polyphenols may affect neurotransmitter systems, particularly gamma-aminobutyric acid (GABA) receptors, which are critical for managing neuronal excitability and preventing seizures. By altering GABAergic activity, polyphenols from mulberry leaves might assist in stabilizing nerve cell function and decreasing the likelihood of seizures. What's more, the antioxidant qualities of these compounds can safeguard neurons against oxidative stress, a condition frequently linked to seizure disorders. Mulberry leaves may also exhibit anti-inflammatory properties that help diminish neuroinflammation, another contributor to seizures. Although animal studies have indicated encouraging anticonvulsant effects, further clinical research involving humans is necessary to thoroughly evaluate their potential as a natural treatment for seizure disorders **[33]**.

6.6 Anti-atherosclerosis: Research has explored the potential anti-atherosclerosis benefits of mulberry leaves. Atherosclerosis is a condition characterized by the buildup of plaque in the arteries, which can lead to cardiovascular issues. These leaves are rich in bioactive compounds such as flavonoids, alkaloids, and polysaccharides. These compounds may assist in lowering lipid levels, reducing inflammation, and preventing oxidative stress, all of which are essential in fighting atherosclerosis. The lipid-lowering properties of mulberry leaves include lowering LDL cholesterol and triglycerides, which greatly contribute to the development of arterial plaque. Their anti-inflammatory effects may help to reduce chronic inflammation, an important factor in the advancement of atherosclerosis. What's more, mulberry leaves are abundant in antioxidants, which help neutralize free radicals and lessen oxidative stress, thereby shielding the arteries from harm. These leaves also aid in regulating blood sugar levels, a benefit that is especially important for those with diabetes, as this condition can often hasten atherosclerosis. While these findings are encouraging, additional clinical studies involving humans are necessary to fully determine the impact of mulberry leaves in preventing or treating atherosclerosis. It is advisable to seek guidance from a healthcare professional before adding it to a treatment plan **[34]**.

6.7 SARS-CoV-2 inhibition: The polyphenols present in mulberry leaves (Morus species) have garnered significant attention for their potential antiviral properties, particularly in inhibiting SARS-CoV-2, the virus responsible for COVID-19. Research indicates that polyphenols, including flavonoids like quercetin, rutin, and kaempferol, as well as phenolic acids such as caffeic acid and gallic acid, may exhibit several mechanisms of action against

SARS-CoV-2. Notably, certain polyphenols can bind to viral proteins, such as the spike protein and main protease (Mpro), thereby blocking the virus's entry into host cells or inhibiting its replication. Additionally, their strong antioxidant properties can mitigate oxidative stress induced by viral infections, enhancing cellular health and improving the immune response. The anti-inflammatory effects of these compounds may help modulate immune responses, potentially reducing the risk of cytokine storms associated with severe COVID-19 cases. Furthermore, polyphenols can influence immune cell activity, promoting the activation and proliferation of cells involved in combating viral infections. Some studies also suggest that polyphenols may affect the expression or activity of ACE2 receptors, which serve as entry points for SARS-CoV-2, thus potentially reducing viral load. While the evidence surrounding the antiviral effects of mulberry leaf polyphenols against SARS-CoV-2 is promising, further research, including clinical trials, is essential to establish their efficacy and potential therapeutic applications in managing COVID-19 **[35]**.

So far, the Centers for Disease Control and Prevention (CDC) has identified no effective treatment for COVID-19. Polyphenols have not been extensively studied in the scientific community for possible antiviral activities besides SARS-CoV-2 yet. It can help lower SARS-CoV-2 mortality and morbidity by giving patients beneficial antiviral or anti-inflammatory treatments. These properties make several naturally occurring polyphenols ideal candidates for use as a preventive drug to reduce viral infection rate and the danger of a virus-caused inflammatory reaction **[36-38]**. Polyphenols have molecular potential as viral protease inhibitors because of their strong hydrogen bonding affinity for proteins and minimal toxicity. They have a strong affinity for proteins and have few harmful side effects. Polyphenol binding to the spike protein may be similar. The Spike protein of coronaviruses is the individual viral membrane protein that allows cells to enter. It explains what viral tropism is by the virus's capacity to bind to the cell membrane. So, the CoV-2 spike protein stops spike-mediated fusion of the membrane, which stops the virus from entering **[39]**.

ACE2 is a potential therapeutic target because it allows SARS-CoV-2 into host cells. A screening investigation found polyphenols promising for ACE2 ligands to prevent virus entry with a strong binding. It may reduce the severity of COVID-19 lung injury by regulating the expression of the antioxidant ACE2 **[40]**.

Research that showed resveratrol stopped the Middle East respiratory syndrome coronavirus (MERS-CoV) from replicating in vitro by blocking the production of nucleocapsid and RNA proteins led to the idea that polyphenols might stop SARS-CoV-2 RdRp. Preclinical and clinical studies are needed to improve the findings, but none are currently happening. Also, the formulation of these polyphenol-based nutraceuticals should be considered. Concerns about low bioavailability and high levels of active polyphenols in the respiratory system, which is where most infections come from, should be addressed with aerosol delivery methods like inhalers and nebulizers **[39]**.

6.8 Antimicrobial activity: Mulberry leaves are rich in polyphenols, including flavonoids and phenolic acids, which show major antimicrobial properties against various pathogens. These polyphenols can inhibit bacterial, fungal, and viral growth by disrupting the membranes of microbial cells, interfering with their enzymatic functions, and diminishing biofilm formation, an essential factor for the survival and virulence of microbes. Research has indicated that substances found in mulberry leaves, such as quercetin, rutin, and chlorogenic acid, are particularly effective against dangerous bacteria like *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhimurium*. Besides, extracts from mulberry leaves have been found to inhibit fungal pathogens, including *Candida albicans*, and to exhibit antiviral properties against specific viral strains. This broad-range antimicrobial activity positions mulberry polyphenols as a promising natural option for infection management and overall health enhancement **[41]**.

6.9. Antioxidative effect: Various results showed that mulberry leaves were highly protective against free radicals and oxidative stress-induced tissue damage. The antioxidant capabilities of mulberry leaf extract have been quantified, showing values ranging from 1.89 to 2.12 mM Trolox equivalent per gram of dried leaves for one measurement method, and a higher range of 6.12 to 9.89 mM Trolox equivalent per gram of dried leaves for another method. The variation in antioxidant capacity between measurement methods suggests the importance of employing different assays to fully assess the antioxidant potential of plant extracts. The extract's ability to donate electrons lowered Fe3 to Fe2. All tests on mulberry leaves demonstrated a dose-dependent antioxidative effect. Previous positive controls, ascorbic acid and butylated hydroxytoluene (BHT), showed a stronger but less apparent effect. Phenoxenic acid and flavonoids have antioxidant effects **[42]**. According to earlier studies, the mulberry leaf extract fractions with the highest phenolic and flavonoid content exhibited the strongest antioxidant activity. This is supported by the substantial link between antioxidant content and efficacy **[43]**.

7. The metabolism of polyphenols

Polyphenols are extensively metabolized in the body's tissues or by bacteria in the intestines, for non-absorbed portions and fractions are re-excreted in bile. Polyphenols are converted to

O-glucuronides, sulfate esters, and O-methyl ethers in the body. Firstly, this conjugation occurs in the intestinal barrier, as evidenced by quercetin perfusion studies in living rats. When tested, quercetin glucuronides (QGs) were generated in the gut mucosa and secreted to the gut lumen or serosal side. Rat's gut has the most glucuronyl transferase activity. The conjugates then travel to the liver to be metabolized and eliminated. Citronella catechins, for example, are heavily methylated. Only half of the catechin perfused into the rat stomach was O-methylated before getting to the liver, whereas the catechin produced in the bile was 99 % catechin. In contrast, only O-methylated in mesenteric plasma was half of the catechin. Except for some flavonoids like phloretin, which was identified in both conjugated (90%) and non-conjugated (10%) forms in rat plasma, plasma contains almost no free aglycones. There were two kinds of phloretin in rat plasma: one that was conjugated and one that wasn't. There were also free flavonoid aglycones in tests that used therapeutic doses of flavonoids, which suggests that the conjugation routes may have been saturated. By joining glucuronides and sulfate groups, these compounds may form anionic derivatives that are quickly flushed out of the body. The biological properties of polyphenol-conjugated derivatives are unknown due to the lack of commercial standards [44] as shown in Figures 3,4, and 5.

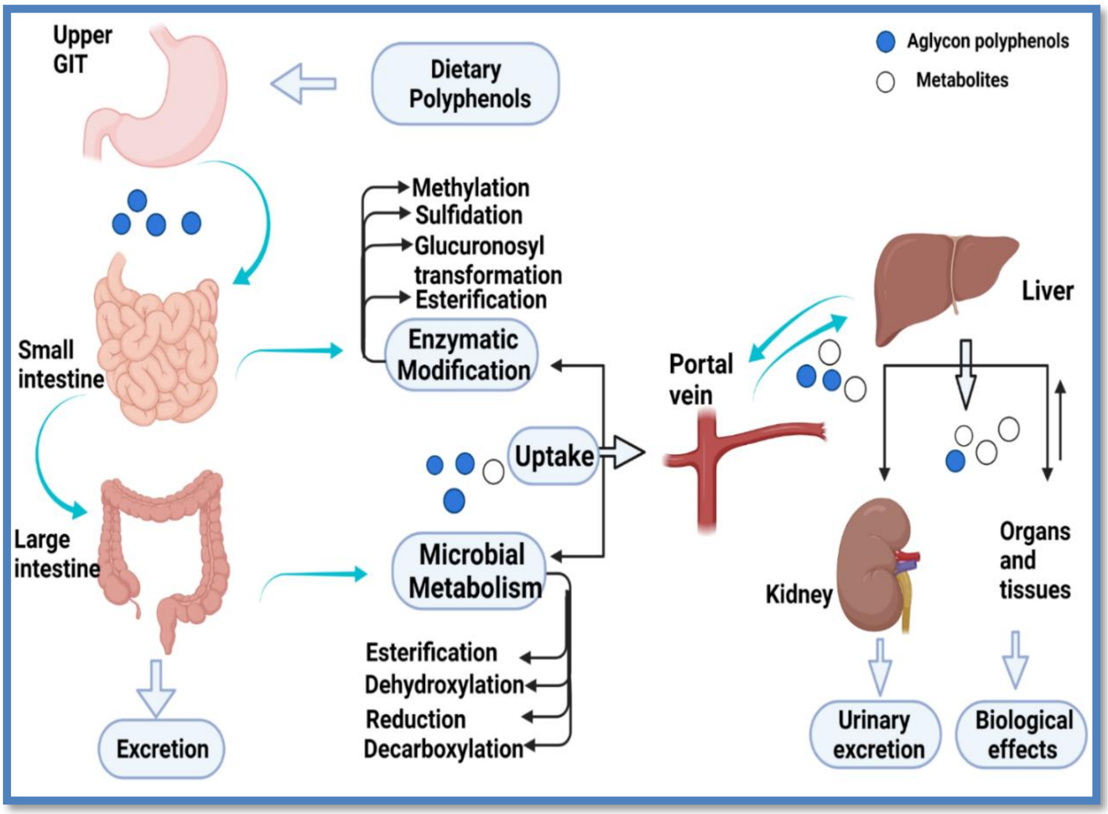

Figure 5: Dietary polyphenols' absorption and metabolism. Aglycon polyphenols are represented by blue dots, and their metabolites are represented by white dots. Adapted with permission from Ref. [44] Copyright 2024, MDPI

8. Food Processing utilization

Mulberry leaves (Morus species) are gaining recognition in food processing due to their rich nutritional and functional properties, offering diverse applications in various products. They can be processed into powders or extracts and utilized as nutraceutical ingredients, thanks to their abundance of bioactive compounds such as flavonoids, polyphenols, vitamins, and minerals. Dried mulberry leaves are also popular in herbal tea production, known for their antioxidant properties and appealing health benefits, making them a preferred choice for natural beverages. Their mild, slightly sweet flavor allows them to serve as natural flavoring agents in a range of food products, including beverages, sauces, and snacks. Additionally, mulberry leaves can provide natural colorants to enhance food aesthetics without synthetic additives and act as natural preservatives, extending the shelf life of products through their antioxidant properties. They can be incorporated into fermented products, promoting the growth of beneficial microorganisms, and added to functional snacks like energy bars and chips, enhancing nutritional profiles and supporting health benefits such as improved blood sugar regulation. Furthermore, mulberry leaves can also be processed into animal feed, contributing essential nutrients to livestock health **[45]**.

Mulberry leaves have emerged as a novel raw material food source. Several studies have been conducted on manufacturing Mulberry leaves-enhanced foods containing ordinary foods, healthy foods, and seasonings, among others (granule beverages, bitter melon, biscuits, and vinegar). The production of Mulberry leaves juice beverages or yogurt attempts to reinvent Mulberry leaves and create healthier and novel foods. When it comes to tea, Mulberry leaves have been utilized for centuries, as documented in the "Compendium of Material Medica." Mulberry tea comes in a variety of flavors and variations in China. Mulberry tea has been established as a local standard in some locations, and two companies have obtained trademark protection for mulberry tea [44]. Mulberry leaves tea can lower blood sugar levels and have antioxidative effects that help stop many ailments. Mulberry leaves were shown to be highly nutritious, with amino acids and polyphenols when fermented with Mauri yeast **[44]**. A methanolic extract of Mulberry leaves improved the storage period of minced beef.

Foods that contain antioxidant chemicals derived from residual sources may have a greater shelf life because they are less susceptible to lipid peroxidation and are less susceptible to oxidative damage because they scavenge oxygen radicals. These effects may also be transferred to people, perhaps increasing the impact of particular foods on human health due to their enhanced antioxidant potential. However, to increase the polyphenol content of plant meals, meticulous control of the production process is required.

Due to the advancement of nano-sized functional food components containing polyphenols, food safety and quality have increased, smart packaging has been developed, targeted distribution of compounds has been achieved, and the sensory qualities of food items have improved. Nanoparticles such as cyclodextrins, gelatin, casein and whey proteins, zein, chitosan, and complex nanoparticles are commonly employed as Nanocarriers in pharmaceuticals and other applications. These carriers protect sensitive polyphenols while also preserving the beneficial polyphenolic properties of the polyphenols. The delivery of these particles is improved due to their nanoscale dimensions. Future research should focus on the validation of suitable methods for the characterization of nanomaterials in complex matrices and measuring their reactivity and in vitro degradation to facilitate safety-risk assessments. For example, nanomaterials such as ENPs, used in food-packaging materials, should be addressed for their potential toxicity. The utilization of native Nanocarriers, such as casein micelles, as an alternative strategy could be explored. The GRAS status of casein micelles has been confirmed. It should be remembered that numerous health benefits associated with polyphenols have not been proven in vivo research, and that the use of polyphenols may be harmful to one's health when consumed in large quantities. Certainly, more people should be educated about nanotechnology and polyphenols and informed of the benefits and concerns associated with them **[46]**.

9. Externalities

9.1 Cultivation area conditions and nitrogen amount: A quantitative study in some Chinese cities shows the difference in the amount of different polyphenolic compounds in both fresh and dried leaves, indicating the temperature's effect on mulberry leaves' polyphenols. The Guangxi area has products with more antioxidant activity than Guangdong and Chongqing. The phenolic compounds are the major compounds with antioxidant activity in mulberry leaves. The different components may be due to different temperatures, as lower temperatures are more suitable for these extracts. The nitrogen amount in the soil also affects the number of different extracts; increasing the nitrogen content decreases both flavonol and chlorogenic acid and increases other materials **[47]**. Harvest and processing times: the levels of polyphenolic compounds decrease with the increase of harvest time, while the amount increases with increasing heat processing time, which must be taken into consideration **[48]**.

9.2 The solvent used for extraction and PH: An experiment proved that the content of polyphenols in methanol extract was more than that in water, ethanol, and acetone, respectively [49]. The most appropriate pH for polyphenolic extraction is the neutral pH [50].

9.3 Temperature: Polyphenolic compounds in mulberries remained almost unchanged at 60° C and below, while decreasing significantly with the temperature above 70° C. The polyphenol extractions are stored at 5 °C in the dark to remain stable for 30 days. Then, the content decreases gradually [49].

9.4 The Economic and Medical Significance of Mulberry: A Source of Antimicrobial, Antioxidant, and Therapeutic Advantages: Mulberry is economically important directly or indirectly due to its important role in the industry, medical, and environmental fields. Mulberry by-products have anti-microbial, anti-hyperglycemic, anti-hyperlipidemic effects, etc., which can be used very well in the pharmaceutical industry [51]. Polyphenols exhibit Gram-positive inhibitory impact, especially toward Bacillus cereus, Staphylococcus aureus, Micrococcus luteus, and Listeria monocytogenes, while having little effect on Gram-negative bacteria as Escherichia coli and Pseudomonas aeruginosa, and no effect on Candida albicans. Some polyphenols inhibit α-amylase as α-amylase activity is connected to its substitution [52]. Polyphenols in mulberries have an antioxidant effect, which can be used in heat stroke. Polyphenols can also be used in treating sore throats. Also, due to the antioxidant effects, polyphenols can be used as anti-aging factors in animal models that need more investigation [53].

9.5 Safety: Many studies on mice were done to see the safety and the side effects of mulberry, but it was proved that mulberry leaf ingestion is safe. An experiment on mice for 2 weeks shows the safety of the leaves' products, and another study on mice for 90 days finds no serious side effects [53].

9.6 Zero waste process: In this process, all materials are in a circular system, meaning the same material will be used many times till almost complete consumption. In this strategy, no product or by-product is wasted. All will be recycled. The zero-waste technique is used in many fields, including agriculture, which means it can be used in mulberry by-products [54].

10. Conclusions

In a circular and sustainable bioeconomy, organic agricultural wastes are utilized as extraction material, and recovery chemicals are reinserted into the production chain. scientists use different recovery procedures to acquire bioactive compounds. Optimization of extraction techniques is required to boost production yields while being environmentally benign and economically viable. The purpose of the recent review was to emphasize the importance and applicability of various contexts of Morus species. It is abundantly obvious from the foregoing discussion that mulberry is a useful medicinal plant with the vitality of tremendous potential. Recently developed approaches to functional applications revealed that Morus species and their bioactive phytochemicals exhibit a varied range of biomedical activities, as well as antioxidants, anti-diabetic, hypolipidemic, anti-obesity, anti-hypertensive, and anti-atherosclerosis, among others. Morus extraction methods, metabolism, and a variety of food industry applications were also discussed. In general, a New study on the phytochemical and pharmacological aspects of Mulberry leaves is needed. Mulberry leaves have several potential applications.

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