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REVIEW

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Therapeutic efficacy of gut microbiota-derived polyphenol metabolite Urolithin A

Shilpa S. Shetty[1*†], Sandeep Shetty[1†] and N. Suchetha Kumari[1*]

Abstract

Background Despite rising public awareness and improvements in diagnostic and treatment methods, there are adverse effects brought on by drug resistance, an increase in overall treatment costs, and unanticipated side effects from pharmaceuticals.

Main body Therefore, efforts for development strategy that is more efficient, more affordable, and more secure are underway. Such a strategy involves employing naturally occurring phytochemicals to delay the beginning, prevent it from happening, or treat it, and it sparks an increase in interest in studies looking for an effective agent in herbs and other plant materials used in traditional medicines. Urolithins are polyphenol chemicals generated by the gut microbiota studied for potential health benefits and have a high bioavailability. After being ingested, urolithins can move throughout the body and mediate in different locations. Urolithins are studied for over 40 years, but their mechanistic role has been explored recently in understanding their potential health benefits.

Short conclusion This review gives an overview of the current Urolithin A research on human health. The findings highlight the importance of exploring the potential of urolithins as a natural compound for therapeutic applications. Elucidating the mechanisms behind the disease process and pinpointing candidate molecules and pathways to target preventive and therapeutic intervention are the need of the hour.

Keywords Urolithins, Ellagic acid, Ellagitannins, Gut microbiota

1 Background

Gut microbiota-derived polyphenol metabolites are urolithins. Ellagitannins (ETs) are D-glucose carbohydrate-modified hexa-hydroxy-diphenol (HHDP) acid esters with complicated chemical structures. They can be polymeric ellagitannins, like sanguiin H-6, which are produced by polymerizing two or more monomeric ET units, or monomeric ellagitannins, like punicalagin, which have a single glucose core with a specific attachment of HHDP groups. They are hydrolyzed to create HHDP and then converted into ellagic acid. Ellagitannins are found in raspberries, walnuts, and pomegranate fruit. Ellagic acid is produced in the stomach by hydrolysis, which the gut microbiota subsequently transforms into urolithins by losing one of its two lactones and removing hydroxyl groups, of which Uro-A is one of the most common. Interindividual differences in gut microbiota composition might be the reason for the different effects of some foods considered health-promoting, for instance, the excellent dispersion in the anticancer effects of pomegranate consumption. The ability to produce urolithin varies significantly between individuals due to variances

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in the microbiome that regulates ET metabolism [1]. Urolithins are further subdivided into subtypes—Urolithin A (Uro-A), Urolithin B (Uro-B), Urolithin C (Uro-C), Urolithin D (Uro-D), and iso-Urolithin A. Among the urolithin subtypes, Uro-A and Uro-B are the major metabolites.

Further, based on the ability to convert ellagic acid and ellagitannins into urolithins, individuals are grouped into three groups called metabotypes—metabotype A is Urolithin A producer, metabotype B is Urolithin A, iso-Urolithin A, and Urolithin B producers, and metabotype O is individuals who do not produce any urolithins (Fig. 1). According to reports, Uro-A and Uro-B have antimicrobial activity against bacteria such as MRSA, carbapenem-resistant A. baumanii, Campylobacter species, S. dysenteriae, and Vibrio cholera, which is essential for the pathogenicity of bacteria [2, 3].

2 Main text

2.1 Materials and method

The methodical scoping review process is used for the study based on five principles: (a) research question definition; (b) pertinent studies (search strategy) determination; (c) choosing eligible studies; (d) charting the data; and (e) compiling, summarizing, and reporting the results with or without consulting experts in the particular field. The authors used a mix of keywords, including "Urolithins," "Cancer," "Health and Disease," "Gut-microbiota," "Ellagic acid," and "Ellagitannins," to search in PubMed, NCBI, Google Scholar, Scopus, and Science Direct for information reported. Using the references of pertinent papers we found more articles. This manuscript contains 50 peer-reviewed studies on urolithins, cancer, and health and disease published between 2010 and 2023. Inclusion criteria include: (1) studies that were conducted on urolithins in vitro and in vivo and their role in human health and disease, (2) studies with rational and scientific evidence, and (3) studies intended to investigate the underlying mechanism of action. Exclusion criteria include (1) studies with inadequate information, (2) studies that are beyond the scope of review, and (3) urolithin studies that have yet to be conducted.

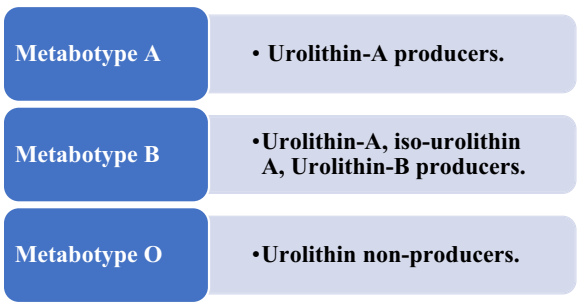

Fig. 1 Metabotypes of urolithin based on the ability of an individual to convert ellagic acid and ellagitannins into urolithins

2.2 Biochemistry and metabolism

Studies have shown that members of the Coriobacteriaceae family *Gordonibacter urolithinfaciens* and *Gordonibacter pamelaeae* contribute to transforming ellagic acids and ellagitannins into Urolithin A. The microbes responsible for the conversion into the final urolithins are still unknown. On consuming ellagitannins or ellagic acid-rich food, pentahydroxy-urolithin (Uro-M5), an essential intermediate product, is produced as the first step in the urolithin metabolite route from ellagic acid via lactone ring opening to form luteic acid. Uro-M5 is the starting point for synthesizing the three tetrahydroxy-urolithins, Uro-D, Uro-M6, and Uro-M7 (Uro-E). Tetrahydroxy-urolithins are then changed into trihydroxy-urolithins, Uro-C, and Uro-M7 are then converted into Uro-A. The major metabolites, dihydroxy-urolithin (Uro-A) and monohydroxy-urolithin (Uro-B), are produced by the final step of the trihydroxy-urolithins (Fig. 2). Ellagic acid had low absorption. However, after consuming foods or juices enriched with ellagic acid, Uro-A and Uro-B were reported to dispersed all over the body. Gut bacteria metabolize ellagitannins to form Uro-A, a member of the chemical compound group dibenzopyrones or benzo-coumarins. These polycyclic aromatic compounds feature a 1-benzopyran moiety and a ketone group linked to the C2 atom (1-benzopyran-2-one). Since the 2000s, early studies on the possible biological consequences of Uro-A have been the main subject of attention. Only some bacteria (Gordonibacter pamelaeae (DSM 19378 T) and Gordonibacter urolithinfaciens (DSM 27213 T) are identified as producers of intermediary urolithins by converting ellagitannins into urolithins, and therefore, its bioavailability largely depends on the makeup of each person's microbiota [2–4]. All ellagitannin-containing foods and medicinal herbs, such as camu camu, arctic bramble, rose hip, sea buckthorn, cranberry, Geranium, and oak-aged spirits, will eventually produce urolithins. Mammals also typically create urolithins by ellagitannin ingestion. Certain urolithin-producing bacteria can influence the health consequences of consuming pomegranates and other ellagitannin foods [1, 4].

2.3 Urolithin A on health and disease

Urolithin A is a major metabolite produced, absorbed in the intestines and available to other body tissues, where it undergoes additional chemical transformations such as methylation, sulfation, or glucuronidation within the hepatocytes and enterocytes (5–7). Uro-A and its derivatives, the most numerous of which are Uro-A glucuronide

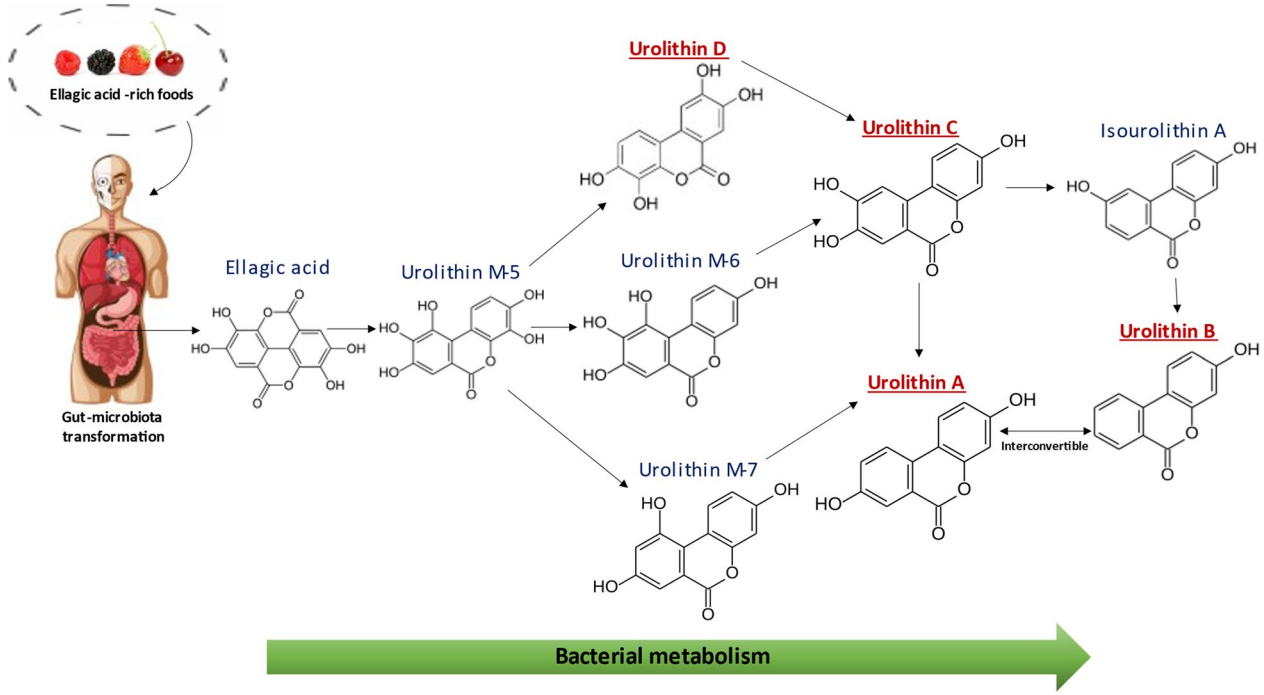

Fig. 2 Catabolic pathway for ellagic acid by intestinal bacteria. This illustration was created with Biorender.com

and Uro-A sulfate, are released into the bloodstream before being eliminated in the urine (6, 7). The importance of Uro-A in metabolic dysfunction, irritable bowel disease (IBD), aging and neurodegenerative diseases are summarized as follows.

2.3.1 Mitophagy and mitochondrial function

Mitophagy is due to mitochondrial destruction by exposure to external inducers. Mitophagy enhances the cellular mitochondrial pool, is intimately linked to the formation of new organelles, and increases mitochondrial respiratory capacity. Uro-A first promotes mitophagy before favoring mitochondrial biogenesis. Uro-A triggers mitophagy and mitochondrial recycling in damaged cells, enhancing the mitochondria's health. Mitophagy is impaired with age advancement and in many age-related disorders [5, 6]. Restoring proper levels of mitophagy is a promising method for halting the deterioration of organ function that comes with aging. Uro-A can trigger several routes that the process uses to progress. Once the phagophore membrane has cleared, the mitochondria, lysosomes, and mitochondria unite [5, 6]. Mitochondrial proteins, including FUNDC1, BNIP3, and others, directly recruit LC3 for the production of autophagosomes in different PINK1—Parkin-independent mitophagy pathways (Fig. 3) [5]. Mitochondrial gene sets were highly expressed in HT-29 colon cells treated with Uro-A. It controls mitochondrial function throughout the body and in skeletal muscle in humans [5] and potentially reverses age-related muscle decline [6].

2.3.2 Anti-inflammatory

The genomic alteration that causes inflammatory disorders is blamed for the pathogenic causes of hereditary and degenerative illnesses. In the race for the anti-inflammatory potential for various disorders, urolithin is a potent anti-inflammatory agent. Uro-A considerably reduced the superoxide production induced by phorbol myristate acetate (PMA) in neutrophils of C57BL/6 mice [8]. Uro-A showed anti-inflammatory efficacy against PMA-induced ear edema. Furthermore, myeloperoxidase (MPO) activity was significantly inhibited by Uro-A [8]. Uro-A showed immunomodulatory effects throughout infection and improved the clinical course of acute campylobacteriosis [9]. The Uro-A-treated group had fewer apoptotic epithelial cells, monocytes, colonic macrophages, and T lymphocytes than the placebo group [9]. Uro-A dramatically lowered serum IL-6 and TNF levels when used as a therapy for LPS-induced peritonitis in the C57BL/6 mice mode l[10]. Tao et al. (2021) [11] described the immunomodulatory effects of Uro-A in a mouse model of osteoporosis by ovariectomy. The TNF-œ, IL-1, and IL-6 concentrations were lowered significantly in the Uro-A-treated group than in the ovariectomized (OVX) control group.

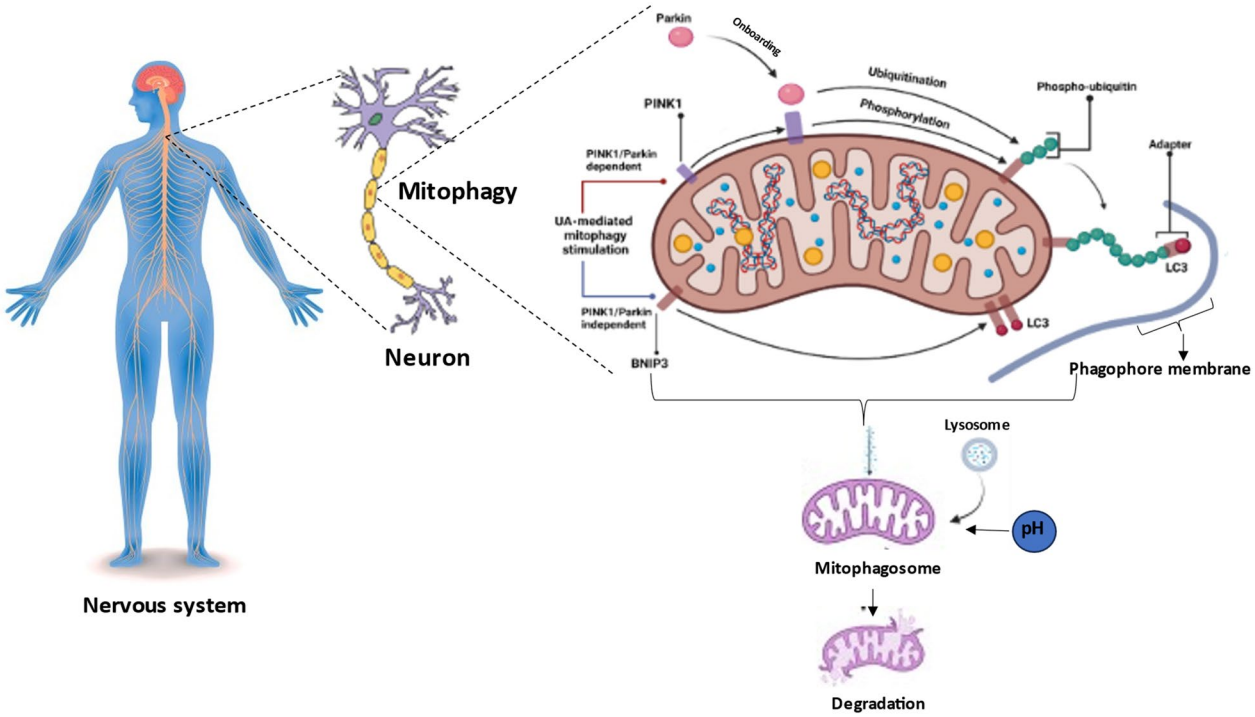

Fig. 3 Mitophagy pathways by Uro-A activates are represented schematically. By maintaining the kinase PINK1 in a stable state, Uro-A triggers PINK1-Parkin-mediated mitophagy (red arrow). Parkin is subsequently brought into PINK1 and ubiquitinates the proteins in the mitochondria. The build-up of phosphorylated mitochondrial proteins results from PINK1's subsequent phosphorylation of ubiquitin chains. By raising mitochondrial BNIP3 (BCL2 Interacting Protein 3) levels, Uro-A activates a PINK1—Parkin-independent pathway (blue arrow). Independently of Parkin and other docking proteins, BNIP3 recruits LC3 (Microtubule-associated protein 1A/1B-light chain 3). It permits the development of a phagosome membrane around the mitochondria for both mitophagy routes. Lysosomes and the originating mitophagosome combine. Low pH and lysosomal hydrolytic enzymes ultimately lead to the demise of the mitochondria. This illustration was created with Biorender.com

Uro-A is the most effective metabolite at reducing inflammation in both primary macrophages and the THP-1 cell line. It demonstrates to dramatically promote ERK1/2 phosphorylation and attenuate NF-B p65 nuclear translocation and phase II metabolism of urolithins, resulting in deactivation. Urolithin glucuronides did not affect the expression or synthesis of any of the investigated signaling proteins, although their capacity to inhibit NF-B p65 nuclear translocation was well demonstrated [12]. Uro-A has an anti-inflammatory effect by lowering the mRNA and protein levels of cyclooxygenase 2 (COX2) and elevating the levels of IL-10 in a rat model of acute colitis and streptozotocin-induced diabetic mice [13]. In macrophages, Urolithin A suppresses TLR3-activated inflammatory and oxidative-associated pathways, and this inhibition is increased by poly(I: C) [14].

2.3.3 Neuroinflammation

In silico and in vivo studies have proved Uro-A's capacity to reduce neuroinflammation and cross the blood–brain barrier (BBB) [15]. Microglia polarize toward a proinflammatory state in a neuroinflammatory environment and generate a stream of proinflammatory cytokines, such as TNF (tumor necrosis factor), IL-6 (interleukin-6), and nitric oxide (NO). These cytokines provide a proinflammatory milieu upon release, which enables protein malfunction, such as that seen in Alzheimer's disease (AD), and unchecked apoptosis [16]. Uro-A decreased IL-1 in the obese mice fed a high-fat diet (HFD) and in the animals given cisplatin to cause nephrotoxic damage. The Uro-A therapy reduced IL-1, IL-6, and TNF levels in the APP (amyloid precursor protein) mice model of AD brains. Uro-A protects against neuroinflammation by promoting the phagocytic activity of microglia by regulating inflammatory responses. PINK1 is required to induce mitophagy, which is how Uro-A decreases neuroinflammation [5]. By guarding against BBB disruption, lowering brain edema, minimizing neuronal apoptosis, and bolstering neuronal autophagy, Uro-A exerts its neuroprotective benefits against TBI (Traumatic brain injury). This lessens the neurological abnormalities brought on by TBI. PI3K/Akt/mTOR and Akt/IKK/NF-B pathway downregulation may contribute to the neuroprotective effects of Uro-A [17].

A link between the severity of Parkinson's disease (PD), gut dysbiosis, and urolithin production was reported [18]. Microbiota-targeted therapies, such as medications, antibiotics, probiotics, and fecal microbiota transplants, may be implemented as new strategies for enhancing diagnosis, avoiding disease progression, and treating it [18]. Ellagic acid (EA), the precursor of urolithin, has proved to protect the brain from the neuronal damage caused by free radicals, which can worsen motor deficits in MFB-lesioned rats [19]. Ellagic acid precursor of urolithin can help manage Parkinson's therapy, as per previous reports [19]. EA has also suppressed glioblastoma growth by regulating Akt and Notch pathways [20, 21].

2.3.4 Aging

Uro-A boosted the life span of worms by 45%, whereas its precursor had no impact. Following these investigations in wild-type worms, Werner syndrome, which causes rapid aging, was modeled using the wrn-1 gene in worms. The double knockout (DKO) mouse model, which exhibits early death comparable to human Duchenne muscular dystrophy (DMD) patients, significantly improved with Uro-A therapy [13]. Uro-A and Uro-B increase muscular strength through multiple mechanisms, indicating their therapeutic and preventive potential in increasing muscle strength in various degenerative and age-related illnesses [22].

2.3.5 Skeletal muscles

Uro-A increases the health span and skeletal muscle function by enhanced muscle fiber integrity, increased mobility, and higher pharyngeal pumping rates in elder worms. Mammals retain the benefits of Uro-A in maintaining muscular health as they age. Uro-A improved the physical endurance, skeletal muscle strength, grip power, and ex vivo tetanic force of MDX and MDX/Utr/DKO dystrophic mice. Young rodents, such as mice and Wistar rats, increased their running behavior after receiving Uro-A supplements [5]. Uro-B boosted testosterone's beneficial effects on skeletal muscle without adversely affecting the body. Uro-B served as a potent regulator of skeletal muscle mass and promoted the growth and differentiation of C2C12 myotubes. It is a possible helpful regulator of skeletal muscle mass because it encourages muscular development and inhibits atrophy [23].

2.3.6 CNS neurodegenerative diseases

In worms that overexpress amyloid beta (A1-42), an APP breakdown precursor that results in toxic aggregates in neurons, Uro-A is neuroprotective and enhances associative memory when exposed to unpleasant stimuli [24]. In the animal model of AD, Uro-A improved learning, memory retention, and neurogenesis. It decreased levels of phosphorylated tau and insoluble A1-42 plaques of AD. It prevented neurological damage by reducing infarct volume in an in vivo model [24].

A recent study on multiple sclerosis (MS) revealed that Uro-A had neuroprotective properties. Early- and late-stage Uro-A treatment decreased the incidence and severity of MS and dendritic cells (DCs), macrophages, and Th17 cells. It also reduces inflammation and white matter demyelination [5, 25]. Uro-B influences the anti-inflammatory, neuroprotective, and antiapoptotic activities of ETs. Inhibition of IL-6, NO, PGE2, TNF, and ROS production by murine BV-2 microglia reduced neuroinflammation [23].

2.3.7 Inflammatory bowel disorders

A chronic DSS-induced IBD model (dextran sulfate sodium inflammatory bowel disorder) Uro-A improved mucosal integrity and reduced colon inflammation markers [5, 26]. It treats diseases characterized by barrier failure, including colon cancer, celiac disease, and irritable bowel syndrome [5, 26]. Acute kidney injury (AKI) is a transient renal injury or failure that needs hemodialysis. Uro-A prevented the tubular damage caused by cisplatin (creatinine). In the kidney, Uro-A treatment reduced the number of tubular cells that underwent apoptosis or the expression of cell death markers (caspase-3 activity). Even cisplatin-administered mice fared better with Uro-A nanoparticles and increased bioavailability [5, 27]. Differentially regulating inflammatory miRNA and cytokine production, Uro-A also inhibited the effects of LPS (lipopolysaccharide) on NOS2 (nitosomines), ROS (reactive oxygen species) generation, intracellular calcium, and DNA double-stranded breaks. Uro-A is a new medicinal agent for managing inflammatory conditions like IBD [28]. Uro-A increases miR-10a-5p expression, reducing SOCE by downregulating Orai1 and STIM1/2 expression. Uro-A is a natural immune suppressant in treating IBD and other inflammatory illnesses by upregulating miR-10a-5p, inhibiting SOCE in mouse CD4+T cells [29].

2.3.8 Diabetes

The most common trait of diabetes is chronic hyperglycemia, with a wide range of adverse effects on the body. Dietary (poly)phenols can serve as suitable nutraceuticals and beneficial adjunct therapies for the management of diabetes and the prevention of its consequences [30, 31]. Urolithin intervention in high-fat diet (HFD) mice enhanced insulin sensitivity and glucose tolerance. In a clinical trial, on diabetic patient consuming concentrated pomegranate juice for eight weeks reduced total cholesterol, LDL (low-density

lipoprotein), cholesterol, the ratio of LDL to HDL (high-density lipoprotein) cholesterol, and the total cholesterol to HDL cholesterol. With noted difficulties with the metabolism of lipids in patients with diabetes, enhancements in these different indicators brought about by urolithin-rich treatments offer convincing evidence for their benefits in treating diabetes [30, 31]. In the pancreas of type 2 diabetes model mice, Uro-A restored the autophagic clearance process and controlled the AKT/mTOR signal, which reduced oxidation, inflammation, and apoptosis [32].

2.3.9 Anticancer effects

2.3.9.1 Cell cycle arrest and apoptosis The human endometrial cancer cell line, Ishikawa, and HEC1A cells showed cell cycle arrest in G2/M by Uro-A. Cyclin-B1, p21, phosphorylated-Cdk1, and CDC25B (cell division cycle 25B) were upregulated and Uro-A downregulated ER. E2 therapy suppressed ER-α (estrogen receptor) and ER-β. By binding to ERE (estrogen-responsive element), Uro-A performed a function akin to an estrogen agonist in the endometrial cancer cells. Intriguingly, the estrogen receptor-positive human breast cancer cell line MCF7 responded to Uro-A in both estrogenic and antiestrogenic ways. In human colorectal cancer cell lines, HCT-116, Uro-A exerts antiproliferative effects by G2/M phase cycle arrest [33]. Uro-A enhances immune cell performance in the fight against cancer [33]. Tumor-fighting immune cells transform into memory T stem cells after Uro-A therapy. Because of their reproduction capacity, they continuously replenish the immune system with fresh, non-exhausted T cells [33]. When a cell encounters issues like DNA damage, apoptosis is triggered. Uro-A promoted apoptosis in human prostate cancer cell line DU-145 [33]. Uro-A prevented the movement of androgen receptors from the cytosol to the nucleus. Human leukemia cell lines MOLT-4 and HL-60, as well as the anaplastic lymphoma cell lines KARPAS-299 and MAC-2A, experienced lower cell growth after exposure to Uro-A and also induced an increase in cell death and reduced phosphorylated Akt. Through CK2 inhibition, Akt was rendered inactive [33]. A drop in phosphorylated Akt caused a rise in apoptotic cells. Utilizing MiaPaCa2 or PANC1, Uro-A treatment prevented tumor volume growth, and cleaved-caspase-3 was elevated in mice xenograft models. Uro-A inhibited PI3K/AKT activation and prevented pathway reactivation in pancreatic ductal carcinoma [33]. EA can act as an anticancer candidate in cancerous B-lymphocytes isolated from CLL (Chronic lymphocytic leukemia) patients by explicit and direct targeting of mitochondria and cause cell death through the ROS-mediated mitochondrial pathway, resulting in cytochrome c release, caspase-3 activations, and apoptosis [34].

2.3.9.2 Cancer metastasis Several anticancer mechanisms have primarily been explored in Uro-A. These processes are mostly linked to the varied effects of Uro-A on intracellular signaling pathways. They help exert direct anticancer effects and anti-inflammatory actions [35]. Recent research revealed that autophagy may boost MMP-9 (Matrix metallopeptidase) and control the spread of cancer. In a human colorectal cancer cell line called sw620, Uro-A reduced MMP-9 (matrix metalloproteinase) activity, hindered motility and invasion, and stimulated autophagy [35]. 3-Methyladenine (3-MA) inhibited autophagy, which counteracted Uro-A's metastasis suppression. Uro-A reduced cell motility and promoted apoptosis by controlling the Akt pathway in the human pancreatic cancer cell lines [35].

2.3.9.3 Inhibiting epithelial–mesenchymal transition (EMT) in lung cancer cells Uro-A changed the phenotype of the lung cancer cell lines A549 and H460 with K-Ras mutations, causing them to adopt a cuboidal epithelial shape with significantly less active filopodia and lamellipodia. Uro-A treatment resulted in less cell invasion into the wound and decreased cell viability in A549 and H460 cells. Western blot analysis on a few proteins associated with EMT indicators supports these findings, suggesting that Uro-A may regulate the EMT function [36, 37].

2.3.9.4 Effect on different cancer types *Prostate cancer* Prostate cancer, one of the fifth cancer of death kinds affecting men, accounts for 20% of all new cancer cases. Urolithins exert their chemopreventive effects on LNCap, DU-145, and PC-3 prostate cancer cell lines, which leads to overexpression of p21, leading to significantly reduced cell development, followed by the cell cycle arrest at the S and G2/M phase, and apoptosis [38]. Prostate-specific antigen (PSA), androgen receptor mRNA level, and expression of proteins undergo temporally dependent declines in growth inhibition. PSA transcription was suppressed due to the decreased contact between the androgen receptor and the reacted element brought on by this reduction. Uro-A raised CDKN1A and p21 protein expression levels, arrested in the G1 phase of the LNCaP cancer cells [33]. Prostate cancer cell lines C4-2B, treated with Uro-A showed cell growth arrest, apoptosis, caspase-3, and PARP (poly(ADP-ribose) polymerases) were activated, thereby inhibiting androgen receptor signaling [39, 40]. Methylated urolithin A (mUA) can reduce cell survival in DU-145 cells by altering miR-21 and its downstream series-wound targets, such as PTEN (phosphatase

and tensin homolog deleted on chromosome 10), Akt, and Wnt/-catenin signaling. This outcome demonstrated the potential of combining Uro-A and Uro-B therapy to enhance prostate cancer's medical management [40].

Breast cancer Breast cancer is the second-leading cause of mortality for women under age 60. Most of the time, the true etiology of breast cancer remains a mystery. Approximately 1 in 10 women worldwide have breast cancer. Chemotherapy, hormone replacement therapy, radiation, and breast tissue removal are currently available therapeutic options [41]. Estrogen is a hormone synthesized from the enzyme aromatase that promotes a rise in breast cancer cell growth and proliferation. Consequently, attempting to inhibit the activity of this enzyme to stop the manufacture of estrogen would be a viable technique to stop the proliferation of breast cancer cells. Uro-B considerably enhanced the suppression of estrogen- and testosterone-induced cell growth, suggesting it is a competitive aromatase inhibitor [23].

In breast cancer MCF-7aro cells, urolithins (Uro-A, Uro-B, mUro-B) have antiproliferative, antiestrogenic, and inhibited hormone-dependent cancer cell proliferation [40]. The proliferation of endogenous SERM 27 hydroxycholesterols can be reduced by pomegranate extract [22].

Uterine cancer Endometrial cancer accounted for almost 7% of all newly diagnosed malignancies in the USA, ranking it fourth among all cancers afflict women. Along with the global increase in obesity rates, it is becoming more common, with twice the rate seen over the previous 20 years. The endometrial cancer treatment includes pelvic node dissection, bilateral salpingo-oophorectomy, and hysterectomy. Endometrial cancer cell proliferation was inhibited in the G2/M phase by Uro-A and Uro-B [41, 42]. Additionally, it boosted the production of proteins such as Myt1 and CDC25B and the G2/M phase regulators cyclin-B1, p21, phospho (p)-CDC2, and cyclin-E2. Uro-A functions as an estrogen agonist and exerts a chemopreventive effect against endometrial cancer via an ERα-dependent mechanism. Uro-A altered the expression of ER-mediated genes such as PGR, pS2, and GREB. Rac1 and PAK1 activity and mRNA levels were considerably decreased, which also caused actin depolymerization, which reduced cancer cell proliferation and migration. Uro-A may play a protective function in the spread of cancer [40]. Ellagic acid significantly reduces ROS production and NHE1 expression, which results in endometrial cancer cells having less Na^+/H^+ exchanger activity, pH, glucose absorption, and lactate release. These outcomes probably help reprogramme tumor cells and slow their proliferation [43].

Hepatocellular carcinoma Hepatocellular carcinoma (HCC) came in second in cancer-related deaths and was placed sixth overall among cancer types. According to reports, 780,000 cases of hepatocellular carcinoma were detected in 2012, leading to 750,000 fatalities having a low 5-year survival rate. HCC develops due to inflammation-induced liver cell damage that results in necrosis and fibrosis. Uro-A and Uro-B can prevent HCC by controlling the Lin28a/let-7a axis and EMT-related targets, including HMGA2 (High Mobility Group AT-Hook 2) and K-Ras. It reduced the proliferation and invasion of HepG2.2.15 cells [44]. The inhibiting Effect is connected to elevated cell cycle protein expression, decreased c-Jun phosphorylation, and programmed cell death regulators like p53 and p38-MAPK. Uro-B hindered the formation of HCC and resulted in repeated cell cycle arrests in HepG2 cells during the G0/G1 phase and in Bel7402 cells at the S phase and also caused apoptosis by decreasing Bcl-2 protein expression. In vivo, a mouse xenograft model, Uro-B, prevented the growth of tumors [38, 40].

Colorectal cancer The primary cause of death around the world is colorectal cancer (CRC) which affects both sexes equally. Cancer incidence and the leading cause of death are rated third and fourth, respectively. It starts as a polyp in the colon's rectal area's internal lining. If untreated, it becomes a cancer cell that can spread to other body parts. Consuming high-calorie foods like animal fat can increase one's risk of developing colon cancer. Urolithins promote cell cycle arrest and cell death in colorectal cancer cells to exhibit their anticancer activity [45]. Uro-A inhibits Wnt and IGF-1 signaling to exert its anticancer effects. Urolithins induce cell cycle arrest and apoptosis in the HT-29 and SW480 colon cancer cell lines by activating caspase-3 during the S and G2/M phases [40]. Uro-A inhibits colon cancer cell growth in vitro and is now markedly supported by a functional p53 and TIGAR induction [46]. The antiproliferative activity of EA and EA metabolites (gallagic acids, Uro-B, and mUro-A) against the human colon cancer cell line HCT-116 was proved [47]. EA treatment demonstrated the chemoprotective role of EA against DMH (1, 2-dimethylhydrazine) induced experimental colon carcinogenesis. Urolithin uses a similar CDKN1A up regulatory mechanism to inhibit colon cancer cells [48]. To alleviate and increase antitumor immunity, UB destroys cancer cells by boosting the activity of NK cells and inhibiting the regulatory T cell's activity. It acts similarly to the dendritic cell vaccination by inhibiting the expression of PD-L1, relieving immunosuppression, promoting antitumor immunity, and upregulating the expression of HLA-B and TCR. It also improves antigen presentation. Thus, urolithin may support anticancer therapies and offer a setting with a robust immune response for further immunotherapy [15].

Bladder cancer One of the most prevalent malignancies in humans, ranked ninth in cancer types. It is a complex illness that, when untreated, is associated with increased morbidity and mortality. The diagnosis includes a medical history, diagnostic tests, imaging, cystoscopic examination, and tissue cytology. Although the initial therapy for bladder cancer is frequently cisplatin, it is accompanied by adverse side effects and medication resistance. On the UMUC3 bladder cancer cell lines, urolithin therapy enhanced genetic instability, uncontrolled cell division, and G2/M phase arrest. In addition to relying on the activation of the ERK pathway, bladder cancer is linked to a malfunction in the PI3K/Akt signaling system, where cancer cells continue to grow and resist apoptosis. Uro-A reduced p-Akt and ERK 1/2 phosphorylation [49].

Leukemia Leukemia continues to be a leading cause of sickness and death worldwide. Leukemic cell lines Jurkat and K562 were considerably affected by Uro-A and Uro-B, with Uro-A exhibiting the most antiproliferative effects. Additionally, leukemic cell metabolism is altered by urolithin treatment, as shown by an increased metabolic rate and noticeable changes in the metabolism of glutamine, one-carbon, lipids, and lactose, as well as well-known pathways involved in energy metabolisms like the glycolysis, Warburg effect, and TCA cycle. Cell growth was slowed down by the increased carnitine levels in leukemic cancer cells treated with urolithin. With this data, new combination medicine can be developed for leukemia [6].

Nasopharyngeal carcinoma Nasopharyngeal carcinoma (NPC) is a frequent malignant head and neck tumor more prevalent in Southeast Asia and Southern China. Radiation and chemotherapy are used as the primary treatment for nasopharyngeal cancer. However, unfavorable side effects, such as radiation angular stomatitis and altered gastrointestinal bacteria, are commonly reported and significantly reduce a patient's quality of lifestyle. According to RNA-sequencing analysis, Uro-A inhibited the ECM receptor interaction pathway and blocked the EMT signaling pathway, which prevented nasopharyngeal cancer cells from proliferating, migrating, and invading. By activating the ROS-mediated mitochondrial apoptosis pathway, Uro-A promotes the death of CNE1 and CNE2 cells and a rise in ROS levels [50].

3 Conclusion

Urolithins are studied for over 40 years, but their mechanistic role has been explored recently in understanding their potential health benefits. These naturally occurring compounds are derived from ellagic acid, a polyphenol in certain fruits and nuts. While ellagic acid itself has been recognized for its antioxidant and anti-inflammatory properties, the metabolites, specifically urolithins, have garnered attention for their potential therapeutic effects. Recent research has shed light on the mechanisms by which urolithins exert their beneficial effects on various aspects of human health. It has been shown that urolithins have high bioavailability. Urolithins can travel to numerous regions of the body and influence a variety of biological processes, including those that are antiobesity, antibacterial, anti-inflammatory, and anticancer. However, further study is required to prove urolithins as a novel, broad-spectrum anticancer chemical for particular tumors. These findings highlight the importance of exploring the potential of urolithins as a natural compound for therapeutic applications. Elucidating the mechanisms behind the disease process and pinpointing candidate molecules and pathways to target preventive and therapeutic intervention is the need of the hour.

Abbreviations

ETS	Ellagitannins
HHDP	Hexa-hydroxy-diphenol
Uro-A	Urolithin A
Uro-B	Urolithin B
Uro-C	Urolithin C
Uro-D	Urolithin D
Uro-M5	Pentahydroxy-urolithin
IBD	Irritable bowel disease
PINK1	Parkin-independent mitophagy pathways
PMA	Phorbol myristate acetate
MPO	Myeloperoxidase
TNF	Tumor necrosis factor
COX2	Cyclooxygenase 2
IL-6	Interleukin-6
NO	Nitric oxide
AD	Alzheimer's disease
HFD	High-fat diet
DKO	Double knockout
DMD	Duchenne muscular dystrophy
DCs	Dendritic cells
NOS2	Nitosomines
LPS	Lipopolysaccharide
CDC25B	Cell division cycle 25B
CLL	Chronic lymphocytic leukemia
MMP-9	Matrix metallopeptidase 9
MA	Methyladenine
EMT	Epithelial–mesenchymal transition
mUA	Methylated Urolithin A
HCC	Hepatocellular carcinoma
HMGA2	High Mobility Group AT-Hook 2
MAPK	Mitogen-activated protein kinases
CRC	Colorectal cancer
NPC	Nasopharyngeal carcinoma

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Author contributions
SSS was involved in conceptualization, methodology, data curation, writing—original draft, and writing—reviewing and editing. SS was responsible for methodology, formal analysis, and writing— reviewing and editing. SKS contributed to conceptualization, and reviewing and editing.

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Availability of data and material
All the data are reported in the manuscript.

Declarations

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The authors declare no competing interest.

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