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# Ellagic Acid – Chemopreventive Role in Oral Cancer

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## Abstract

Ellagic acid is an antioxidant and an anti-proliferative compound present in fruits, nuts and vegetables. In spite of evidences for anticancer activity in various cancer cell-lines, human cancer cells, the mechanistic role of ellagic acid is not conclusive enough to be recommended for a clinical use. The present review provides information about the chemopreventive role of ellagic acid in oral cancer and proposes molecular basis for ellagic acid's inhibitory activity against oral cancer. We show that ellagic acid modulates growth of tumor cells through regulation of multiple cell signaling pathways including cell proliferation pathway (cyclin dependent kinase 2, cyclin A2, cyclin B1, cyclin D1, c-myc, PKCα), cell survival/apoptosis pathway (Bcl-XL, Bax, Caspase 9/3, Akt), tumor suppressor pathway (p53, p21), inflaming Metastasis pathways (IL-1 beta, TNF-α, matrix metalloproteinases 9/3, COX-2), angiogenesis pathways (VEGF), cell immortalization (TERT), NF-κβ.

**Keywords:** Oral cancer; Ellagic acid; Ellagitannins; Urolithins; Angiogenesis; Molecular targets; Cancer hallmarks

## Introduction

Oral cancer is the 10th most common form of cancer worldwide. Developing countries share major global burden of deaths due to oral cancer; countries like India contributes ~ 26% of global oral cancer incidence. Oral cancer is 2nd most common form of cancer among Indian males [1]. Oral cancer is a multi-factorial disease which has implicating attributes like genetics, environmental, life-style and behavioral [2]. Around half of the patients detected for oral cancer will die within 5 years of initial diagnosis. Five year survival rate has not improved in spite of better understanding of cancer at a molecular level and with the advent of rationally targeted drugs [3].

Oral cancer is managed through various approaches like surgery and radiation, which can be used alone or in combination, often with chemotherapy. Chemotherapeutic drugs come with a downside of indiscriminately killing normal cells along with the intended cancer cells. Newer therapeutic approaches use targeted drugs to specifically target cancer cell by exploiting subtle differences between cell types at a molecular level. Such targeted drugs approved for oral cancer treatment, works by targeting important events associated with oral carcinogenesis; blocker agent like Cetuximab [4] acts by blocking entry of growth factor through epidermal growth factor receptor (EGFR), which thereby prevents tumorous cell growth, another set of agents like Bevacizumab acts by targeting vascular endothelial growth factor (VEGF), a critical biomolecule necessary for angiogenesis. The efficacy of these targeted agents has been demonstrated to depend on presence of certain genetic profile. The presence of wild type KRAS is known to be positive efficacy biomarker for Cetuximab. The US Food and Drug Administration (FDA) updated the labels of Cetuximab to include information about KRAS mutations [5]. Such genetic testing often requires development of companion diagnostics to profile patient who is likely to respond positively when treated with targeted drugs [6], however, only large pharmaceutical companies have ventured in the area of companion diagnostics because of factors like cost, complex approval system [7]. Pharmaceutical companies involved in development of targeted therapies will have to invest more when compared with traditional drug development cost; moreover market size will be restricted to smaller patient population who would meet stringent genetic criteria. End-users will have to bear cost of such heavy investment associated with targeted therapies. Widespread use of such targeted drugs in case of oral cancer does not look feasible, since oral cancer is more prevalent in less developed countries in which patients cannot afford such costly treatment. Success of targeted therapy is often limited by acquired drug resistance [8-14], which essentially means constant evolution of targeted therapies.

Nature is a source of anti-cancer compounds which are used as preventive and/or curative agents which act as antioxidants, anti-proliferative agents with general acceptance as a dietary element with a well-established safety profile. According to one of the estimates by World Health Organization approximately 80% of the world's population relies on traditional medicine for their primary health care [15]. Drugs derived from these natural sources have become potential source of alternative medicine which can be used along or in combination with chemotherapy/targeted drugs to manage cancer. Some of the compounds from various natural sources which have shown potential for prevention of oral carcinogenesis are curcumin [16], green tea extract [17,18], luteolin [19], genistein [20], ellagic acid [21], lycopene [22], betulinic acid [23], n-3 polyunsaturated fatty acids [24], hesperetin [25], and 13-cis-retinoic acid [26].

Ellagic acid (Figure 1) is a potent plant antioxidant [27,28] and anti-proliferative [29,30] compound found in numerous fruits, nuts and vegetables including pomegranates, pecans, raspberries, strawberries, walnuts. Ellagic acid (EA) is derived from ellagitannins (ETs) present as dietary polyphenols found in fruits and nuts [31-33]. Ellagic acid

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is further metabolically converted into urolithins by intestinal micro-flora. The various pharmacological properties attributed to ellagic acid are due to ellagic acid alone, or their metabolite, or the combination of both, is still not precisely known.

The anti-proliferative properties of ellagic acid are due to its ability to directly inhibit the DNA binding of certain carcinogens, including polycyclic aromatic hydrocarbons [34], and nitrosamines [35-37]. Ellagic acid down-regulates insulin-like growth factor (IGF-II) [38] and activates expression of tumor suppressor genes p53/p21, leading to cell cycle arrest at the G1/S phase and apoptosis [30]. Ellagic acid prevents carcinogen induced tumorigenesis by activating detoxifying enzymes [39] and inhibiting certain cytochrome P450 enzymes involved in the generation of mutagens [40,41].

Anticarcinogenic effect of ellagic acid have been reported in prostate [42], liver [43], colorectal [38], esophageal [44], bladder [45] and leukemia [46,47] cancer cell lines. Ellagic acid was reported to reduce chemotherapy induced toxicity in hormone refractory prostate cancer (HRPC) [48].

Ellagic acid was reported to inhibit 4-nitroquinoline-1-oxide (4-NQO)-induced tongue carcinogenesis in rat [49] and it also inhibited the growth of premalignant and malignant oral human cell-line [21]. Ohio State University scientists have demonstrated preventive role of ellagic acid in context for oral tumorigenesis [50], their research work is extended to clinical trial with an objective to understand mechanistic details of therapy and design alternative therapy for managing oral cancers [51]. The lyophilized black raspberries (LBRs), consisting of concentrates of nutrients including ellagic acid and anthocyanins, demonstrated to have a protective effect on chemically induced cancer in the hamster cheek pouch [50]. The localized delivery of LMRs with a mucoadhesive gel was evaluated in phase I study with a satisfactory result [52]. Further, the effects of topical application of the 10% black raspberry gel to oral intraepithelial neoplastic lesions in 17 patients and normal tissues in 10 patients was assessed [53]. The significant reduction in loss of heterozygosity at three tumor suppressor gene (p53, CDKN2A, FHIT) loci with histological regression of the intraepithelial neoplastic lesions was observed. The efficacy of chemopreventive role of LBRs was corroborated by gene expression studies, in which reduced expression of COX-2, iNOS, and genes associated with inhibition of apoptosis, RNA processing, and growth factor recycling was observed [54]. The LBRs consist of ellagic acid along with various other nutrients;

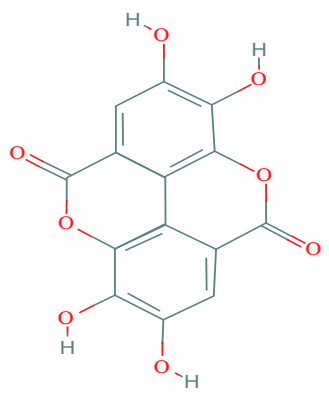


**Figure 1:** Chemical structure of ellagic acid.

therefore caution should be used while assigning pharmacological activities of LBRs to ellagic acid alone. Therefore, future clinical trials are warranted to validate the chemopreventive role of ellagic acid in oral cancer.

This review aims to discuss molecular targets of ellagic acid possibly responsible for prevention of oral cancer and attempts to lay foundation for designing experiments to validate proposed molecular targets of ellagic acid in context of oral cancer.

## Molecular Targets

The chemopreventive role of dietary polyphenols like ellagitannins (ETs) or ellagic acid (EA) can be understood by review of its molecular targets. There is no evidence till date to explain mechanistic details of chemopreventive role of EA in oral cancer (Figure 2). In absence of such direct evidences, we have attempted to propose inference based explanation for chemopreventive role of EA in oral cancer [21,49].

### Casein kinase 2 (CK2)

Casein kinase II (CK2) is a constitutively active serine/threonine protein kinase which is proposed to have regulatory function in cell differentiation, cell proliferation, apoptosis and invasion [55-57]. CK2 can phosphorylate host of intracellular signaling proteins implicated in tumor suppression (p53 [58] and PTEN [59]), tumorigenesis (c-Myc [60], Jun [61], NF-κB [62]). Inhibition of CK2 is suggested to be an attractive therapeutic strategy to manage tumorigenesis in oral cancer [63,64]. Ellagic acid was reported to be a potent inhibitor of CK2 in virtual screening study [65]. The crystallographic structure of α-subunit of CK2 complexed with ellagic acid, has been submitted into the Protein Data Bank (PDB) with entry code of 2ZJW [66]. The availability of structural information should help in understanding details of ligand-receptor binding and thereby should enable rational drug designing [67].

### Telomerase reverse transcriptase (TERT)

Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by addition of the telomere repeat TTAGGG. The enzyme consists of a protein component with reverse transcriptase activity, encoded by this gene, and RNA component which serves as a template for the telomere repeat. The replicative potential of cell is limited by factors like senescence and crisis, which eventually leads to massive cell death by end-to-end fusion of chromosomes, with very rare variants having ability to multiply without limit; the process is termed as *immortalization* [68]. Telomerase activity is critical for controlling unlimited potential for division or immortalization [69,70]. Telomerase activity is not undetectable in normal somatic cells, however can be evaluated in biopsied tissue from oral cancer [71-73]. Recently, dendrimers-delivered shRNA targeting of hTERT has demonstrated to inhibit oral cancer cell growth [74]. Ellagic acid was reported to down-regulate the 17beta-estradiol-induced hTERT expression [75].

### Growth factors signaling pathways

Mitogenic growth signals are required by normal cells to move from quiescent state into an active proliferative state. In normal cell these mitogenic growth factors are made by one cell type in order to stimulate proliferation of another (heterotypic signaling), whereas cancer cells acquire the ability to synthesize growth factors necessary for its own proliferation (autocrine signaling). The suppression of

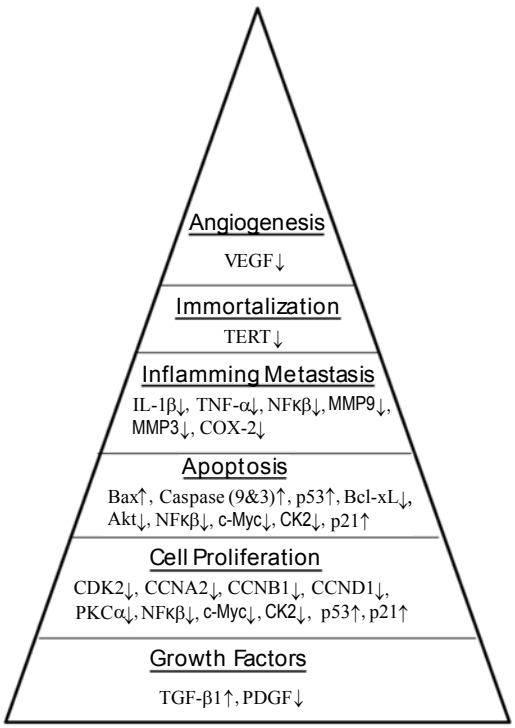



**Figure 2:** Schematic diagram indicating the plausible anti-cancer activity of ellagic acid. Modulation of targets from various cancer hallmarks by ellagic acid. Targets up-regulated is suffixed by ↑, those down-regulated are suffixed by ↓. *TGF-β1* transforming growth factor beta, PDGF platelet derived growth factor, *CDK2* cyclin dependent kinase 2, *CCNA2* cyclin A2, *CCNB1* cyclin B1, *CCND1* cyclin D1, *PKCα* protein kinase C alpha, *Bax* bcl2-associated X protein, *p53* tumor protein p53, *Bcl-xL* bcl2-like 1, *Akt* v-akt murine thymoma viral oncogene homolog 1, *NF-κβ* Nuclear factor-kappa B, *c-Myc* v-myc myelocytomatosis viral oncogene homolog (avian), *p21* cyclin-dependent kinase inhibitor 1A (p21, Cip1), *CK2* Casein kinase 2, *TERT* Telomerase reverse transcriptase, *IL-1 beta* interleukin 1, beta, *TNF-alpha* tumor necrosis factor, *MMP9* matrix metalloproteinase 9, *MMP3* matrix metalloproteinase 3, *COX-2* prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase), *VEGF* vascular endothelial growth factor.

growth factors results in suppression of tumor growth. Growth factors implicated in oral carcinogenesis and targeted by ellagic acid are transforming growth factor-β (TGF-β1) [76] and platelet derived growth factor (PDGF) [77]. Ellagic acid improves expression of TGF-β1, thereby promoting its tumor suppressing activity [78]. Ellagic acid down-regulates expression of PDGF, which is commonly over-expressed in oral cancer [79].

### Nuclear factor-kappa B (NF-κβ)

NF-κβ is a pleiotropic transcription factor found in all cell types. Under resting condition, the NF-κβ dimers reside in cytoplasm. NF-κβ is activated by free radicals, cytokines, carcinogens, inflammatory stimuli, radiation, and endotoxins. Upon activation, it is translocated to the nucleus, where it activates expression of more than 400 genes [80] which are involved in various tumorigenic activities like survival, proliferation, invasion, metastasis, inflammation and resistance [81-84]. NF-κβ promotes cancer development by activating survival genes like Bcl-2, Bcl-XL and also induces expression of critical genes like matrix metalloproteases (MMP) and vascular endothelial growth factor (VEGF) involved in metastasis and angiogenesis. Ellagic acid is reported to be potent inhibitor of NF-κβ [85,86]. Ellagic acid induces apoptosis through inhibition of NF-κβ [86].

### Cell cycle

Cell cycle is tightly regulated event controlled through various check-points to maintain cellular integrity. Cyclin-dependent kinases (CDKs) are the key regulatory enzymes, each consisting of a catalytic CDK and activating cyclin subunits. CDKs regulate the cell's progression through the phases of the cell cycle by modulating the activity of key substrates. Regulatory proteins targeted by ellagic acid which are also implicated in oral carcinogenesis are cyclin dependent kinase 2 (CDK2) [87], cyclin A2 (CCNA2) [88], cyclin B1 (CCNB1) [89], cyclin D1 (CCND1) [90] and protein kinase C alpha (PKCα) [91]. Over expression of these regulatory proteins is hallmark of oral cancer. Ellagic acid induces G0/G1-phase arrest of the cell cycle by decreasing expression of CDK2 [45], S-phase cell cycle arrest by down-regulation of expression of cyclin A and B1 [92] and cell cycle arrest by down-regulation of PKCα [76], cyclin D1 [77].

### Apoptosis and survival pathways

Apoptosis is a cellular mechanism through which natural balance between cell death and cell renewal is maintained by killing damaged, excess, or abnormal cells. The programmed cell death or apoptosis is the mechanism which is triggered by a variety of physiologic signals like DNA damage, signaling imbalance, survival factor insufficiency, hypoxia [93-95], and followed by precise steps, by which cellular components are degraded and removed from the system in less than 24 hrs [96]. Tumor cell have acquired ability to evade such apoptotic actions by promoting anti-apoptotic or survival mechanism. Ellagic acid promotes apoptosis in oral cancer cells, by activating pro-apoptotic genes like Bax [96], Caspase 9 [92], Caspase 3 [92,97] and inhibiting survival genes like Bcl-XL [92], Akt [97], NF-κβ [86].

### Inflaming metastasis pathways

Metastasis is one of the adaptive mechanisms of tumor cells by which they migrate and invade adjacent tissues thereby travels to distant sites, to find new source of nutrients necessary for growth. Ability to metastasize is rendered to tumor cells with intrinsic properties and factors derived from tumor micro-environment such as inflammation [98,99]. Metastasis makes it very difficult to manage cancers, and is one of the most important contributors of deaths caused due to cancer. Ellagic acid inhibits pro-inflammatory cytokines (IL-1 beta [100], TNF-alpha [100]), matrix metalloproteinases (MMP9 [77], MMP2 [101]), COX-2 [77] in oral cancer cells, and there by abrogates metastasis induced by inflammation [99,102,103].

### Angiogenesis

Cell function and survival, critically depends on availability of oxygen and nutrients supplied by vasculature, obligating virtually all cells in a tissue to reside close to blood capillary system. Factors promoting growth of new blood vessels (angiogenesis) is imperative for tumorigenesis. Ellagic acid down-regulates vascular endothelial growth factor (VEGF) [77], a key regulator of angiogenic pathway in oral cancer. Ellagic acid down-regulates VEGF, through indirect pathway by modulating NF-κβ.

### Tumor-suppressor gene p53 and Proto-oncogene c-Myc

p53 occupies critical place in a network of signaling pathways that are essential for regulation of cell growth and apoptosis induced

by genotoxic and non-genotoxic stresses [104,105]. It activates the transcription of pro-apoptotic genes like p21WAF1 [106] and Bax [107] and therefore induces apoptosis.

The p53 induced apoptosis, typically follows intrinsic pathway, however it also modulates apoptosis through extrinsic pathway. p53 brings out apoptosis mainly through transcriptional regulation of apoptosis effectors genes. It activates transcription of various proapoptotic genes like Noxa, Puma, Bax, Bad, and Bim and is also involved in transcriptional repression of anti-apoptotic factors like survivin, Bcl-2, Bcl-XL. It induces apoptosis by transcriptional activation of APAF1 contributing towards formation of 'apoptosome' and also activates death receptors (TNF-α, Fas, DR5), thereby promoting extrinsic pathway. Ellagic acid is known to increase expression of p53 and p21 [45] and induce cell cycle arrest and apoptosis.

c-Myc proto-oncogene is aberrantly expressed in oral cancer [108,109]. c-Myc promotes cell growth by inducing transcription of host of genes involved in cell cycle, apoptosis, DNA metabolism [110,111]. Ellagic acid inhibits cancer cell growth, by reducing the expression of c-Myc [77].

### Antioxidant

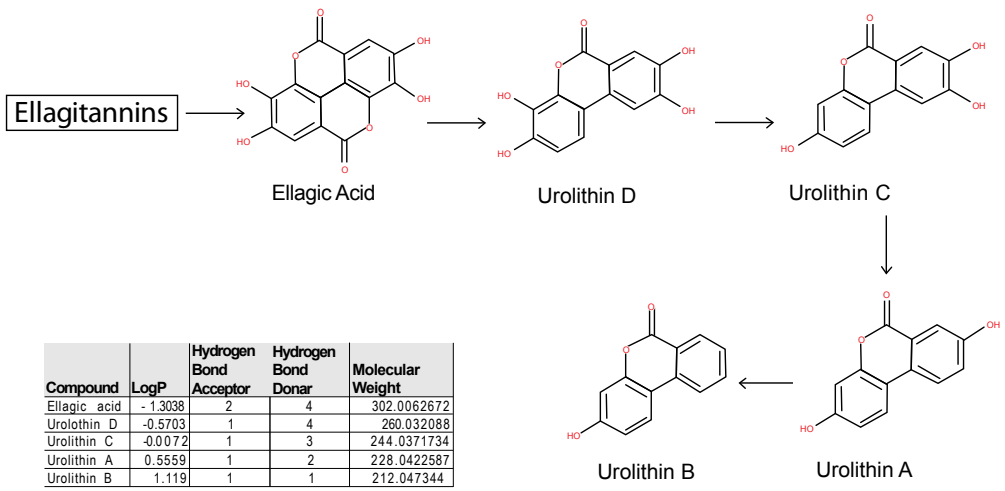
Reactive oxygen species (ROS) are a major cause of cellular injury leading to pathogenesis of various diseases including cancer. The oxidative stress caused by the accumulation of ROS may cause mutagenesis, cytotoxicity and gene expression promoting carcinogenesis in oral cancer [112]. The increase in peroxidation of membrane lipid and ROS has been reported in oral cancer [113,114]. The anti-oxidant enzymes such as superoxide dismutases (SOD), catalase (CAT), glutathione peroxidase (GPX), limit cell injury induced by ROS. The activity of these anti-oxidant enzymes is reduced significantly in tissue samples collected from oral cancer patients [115,116]. Ellagic acid showed high DPPH free radical scavenging and lipid peroxidation inhibitory activities [97,117]. Ellagic acid activates anti-oxidant enzymes such as superoxide dismutases (SOD), catalase (CAT), and glutathione peroxidase (GPX) [97].

## Metabolism and Bioavailability

Ellagitannins (ETs) are hydrolyzed to ellagic acid (EA) *in vivo* under physiological conditions. The presence of ellagic acid in human plasma with maximum concentration of 31.9 ng/ml after consumption of pomegranate juice was reported (at a dose containing 25 mg ellagic acid and 318 mg hydrolyzable ellagitannins) [118]. Ellagic acid is further progressively metabolized by intestinal microbiota into different types to urolithins (Figure 3) *viz.* urolithin D (UD), urolithin C (UC) and finally into urolithin A (UA) and urolithin B (UB) [119]. The urolithin A (UA) and urolithin B (UB) were reported to be the most prevalent metabolites of ellagic acid in human subjects, which persists up to 56 hrs after ingestion of ellagitannins [120-122].

It was observed in pharmacokinetic studies that when mice administered with pomegranate extract or urolithin A, metabolites of ellagitannin (ellagic acid and urolithin A) showed preference to be accumulated in certain organ systems like prostate, intestine and colon [123]. It was further reported that the main metabolite detected was urolithin A glucuronide, (3, 8-dihydroxy-6H-dibenzo[b,d]pyran-6-one glucuronide) (up to 2 ng/g) together with the traces of urolithin B glucuronide, (3-hydroxy-6H-dibenzo[b,d]pyran-6-one glucuronide) and dimethyl ellagic acid of ellagitanins in prostate gland among human subjects [124]. The low bioavailability of ellagic acid should be regarded as one of the major reasons why potent pharmacological activities reported during *in vitro* studies are not replicated in *in vivo* studies. The chemistry development kit (CDK) [125] was used to compute LogP of ellagic acid and urolithins to understand their bioavailabilities. The LogP is a standard parameter used to estimate lipophilicity of the test compound. The LogP values of urolithin A (UA) and urolithin B (UB) is more than zero and close to that required for optimum colonic absorption (LogP = 1.32), explaining their uptake from intestine and entry into systemic circulation.

Some of the pharmacological activities of ellagic acid can be attributed to its metabolic products (urolithins). The antioxidant activity of ellagitannins, ellagic acid and its intestinal microbial metabolites, was studied using a cell-based assay [126]. The urolithins




| Compound | LogP | Hydrogen Bond Acceptor | Hydrogen Bond Donar | Molecular Weight |
|---|---|---|---|---|
| Ellagic acid | - 1.3038 | 2 | 4 | 302.0062672 |
| Urolothin D | -0.5703 | 1 | 4 | 260.032088 |
| Urolithin C | -0.0072 | 1 | 3 | 244.0371734 |
| Urolithin A | 0.5559 | 1 | 2 | 228.0422587 |
| Urolithin B | 1.119 | 1 | 1 | 212.047344 |

**Figure 3:** Metabolism of ellagic acid. Ellagitannins are derived from natural sources like fruits, nuts and vegetables. Ellagitannins are hydrolyzable polyphenols which are converted into ellagic acid *in vivo* under physiological conditions. Ellagic acid is further acted upon by intestinal microbiota, and consequently converted into Urolithin D, Urolithin C, Urolithin A, Urolithin B progressively. Physicochemical parameters of ellagic acid computed by chemistry development kit (CDK) are represented in the Table.

were reported to possess stronger antioxidant activity when compared with parent ellagic acid and ellagitannins. The most potent antioxidants reported were urolithins C and D with IC (50) values of 0.16 and 0.33 microM, respectively, when compared to IC (50) values of 1.1 and 1.4 microM of the parent ellagic acid and punicalagins, respectively. The dihydroxylated urolithin A showed weaker antioxidant activity, with an IC (50) value 13.6 microM, however, the potency was within the range of urolithin A plasma concentrations. The anti-inflammatory and antioxidant activity of urolithin A was also reported in an *in vivo* study [127]. The Urolithin B was reported to have potent anti estogenic activity [128].

## Conclusion

Oral cancer develops by complex interplay between intrinsic and extrinsic factors playing important role in tumor development from primary lesion. The process of expression of tumorigenesis is based on a tightly controlled sequence of events which are dependent on the proper levels of transcription and translation of certain genes. There is a small subset that seems to be particularly important in the prevention, development, and progression of cancer. These genes have been found to be either malfunctioning or non-functioning in oral cancer. It is, therefore, logical to believe that success of any therapy will depend on its effectiveness to modulate these genes controlling different pathways to restore homeostasis. Molecular targets of ellagic acid are the key regulators, spread across all cancer hallmarks, which should make it an effective agent for prevention of oral cancer. Ellagic acid is known to modulate key regulators like NF-κβ, p53 and CK2. The versatility of EA to inhibit oral carcinogenesis through multiple pathways makes ellagic acid a potent chemopreventive agent [129,130].

Low bioavailability of ellagic acid could be one of the major reasons why it was not researched for chemoprevention of oral cancer. The focus of current research has moved to bioavailable metabolites of ellagic acid. We have attempted to present inference based framework to explain role of ellagic acid in prevention of oral carcinogenesis. Structural optimization of ellagic acid to improve its bioavailability does not look promising strategy, as any structural change may significantly alter its anticarcinogenic actions [131]. Advancements in the field of targeted drug delivery system can be used to overcome this challenge [132]. Feasibility of functionalized graphene oxide as nanocarrier for ellagic acid was reported [133]. With this encouraging development in the area of targeted drug delivery system, now it has become possible to design experiments, to understand the pharmacological properties of ellagic acid and its metabolites like urolithins, administered separately or in combination. Such experiments should act as guide to plan clinical trials for testing efficacy of ellagic acid in prevention of oral cancer.

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