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Apoptotic Activity by Chemo-preventive Natural Compounds against Oral Squamous Cell Carcinoma

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Authors' contributions

This work was carried out in collaboration among all authors. Authors NR, NV & RM managed the literature searches. Authors NS and NV wrote the first draft of the manuscript. Author RM also helped in the analysis part. Author AKJ designed the outline of the manuscript and modified it into the final draft. All authors read and approved the final manuscript.

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ABSTRACT

The general frequency and mortality consisting of Oral Squamous Cell Carcinoma (OSCC) is very high and the overall number of oral cancers has been consistently increasing in the world. Oral Squamous Cell Carcinoma (OSCC) is the most typical variety of oral cancer; it causes damage to oral epithelial cells due to accumulation consisting of multiple genetic changes in the cells. OSCC continues to be major cause of mortality in sufferers along with head and neck cancers. Alcohol, smoking and tobacco chewing alone or as well as smokeless tobacco and betel quid are potential carcinogens which contribute to the far natural event of OSCC. The current review focuses on apoptosis induction in human Oral Squamous Cell Carcinoma (OSCC) cells. Several natural products, chemotherapeutic drugs metabolic inhibitors, gene manipulations and hormone receptor ligands cause the general programmed cell death immediately or not directly via relapsing the anti-apoptotic pathways. The main focus of this review is on Apoptotic activities caused by Natural compounds in OSCC which provide us a chemoprevention against cancer.

Keywords: Receptor; oral cancer; metabolic inhibitors; genetic mutations.

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1. INTRODUCTION

Cancer is the commonest cause of death in adult; this disease refers to the uncontrolled growth of abnormal cells anywhere in a body. Oral cancer refers to cancer occurring between the vermilion border of lips and the junction of the hard and soft palates or the posterior one third of the tongue [1]. Over 95% of people with Oral squamous cell carcinoma smoke tobacco, drink alcohol, or both. Some other reasons like impaired ability to repair DNA damaged by mutagens, deficiencies of Vitamin A,E or C or trace elements can also cause OSCC. Oral squamous cell carcinoma develop in almost 65,000 people in the United States per year. In India, 90-95% of the oral cancers is squamous cell carcinoma. National Institute of Health and Family Welfare specified than India alone accounts for 80% of the total Oral cancer figure across the world. This is considered as the sixth most common cancer and accounts for 6% of all cancers in worldwide. More than 30,000 new oral cancers diagnosed each year. Overall, 60% of people with oral cancer will survive for five years or more the earlier the stage at diagnosis, the higher the cancer of survival after treatment.

Apoptosis or programmed cell death (prosses which promote self-degradation of damaged and disinfected cells in body) has become a hallmark for the treatment of many diseases which cause very harmful effects in human being. The term “apoptosis” was first introduced by Kerr et al. It is an active, inherently programmed phenomenon which can be initiated or inhibited by a variety of environmental stimuli, both physiological and pathological**.** Nowadays its becomes a center of attraction of many cell biologist as they want to use specify of this process for targeting a particular cell type. The mechanism of apoptosis occurs in various steps and any small change can disturb the whole scenario and becomes the reason of any type of cancer.

The Study shows, from ancient time lots of natural compounds had been used for treating many diseases. Many effective medicines are made up from natural compounds and also play important role in the field of pharmaceutical and research. Generally cell growth regulation and there disruptions remain normal either there are no disturbance of factors and inducing mutation. These disturbance changes undergo apoptosis and normal cells become cancer cells. In this review the study which is compile is shows how natural compound prevent cells from these factors by inhibiting their effect on apoptosis and OSCC cancer.

2. CELL DEATH PROGRAMME

Apoptosis is a regular occurring process in body which refers to organized death of damaged and disinfected cells under physiological conditions. The process gets affected by some factors like environmental change, hormonal secretion and decreased mass of growth factors. An average of cells consumption by apoptotic process is 50 -70 billion in mature human body in a day. while in children the average decrease till 20-30 billion in a day. Apoptosis take place by two different pathways:

Extrinsic Pathway-Extrinsic pathway was regulated by the death receptor which contains Fas receptor, tumor necrosis factor receptors (TNF), and TNF related apoptosis-inducing legend (TRIAL) receptors [2]. These receptors binds with extrinsic legends and common intercellular information get disturbed and several caspases (cystein-aspartic protease-which control the whole process of apoptosis by signaling, initiation and regulation of the prosses) like protease affect cell function and this disturbance in cells regulatory function condemned death of cell.

Intrinsic Pathway-Intrinsic pathway takes place in mitochondria because of exogenous and endogenous factors like DNA damage and oxidative changes. The intrinsic pathway was influenced by members of the bcl family bound to the mitochondrial membrane, including Bax and Bcl-2, which acts as pro-or antiapoptotic regulatory proteins [3]. These apoptotic proteins release cytochrome C in cell and release caspases activated protein which starts the activity of caspase 9 and caspase 3 &7 get active and becomes the reason of cell death.

2.1 Autophagy

Some cells like Lysosomes contains property of self-degradation or self-lysis of proteins, organelles and some type of bacteria. The autophagy pathway is useful for curing several diseases for example neurodegeneration, myopathy, liver disease and diabetes.

2.2 Necrosis

Necrosis refers to premature death of cells by self digestion because of some enzymatic

change in the environment of cell, this change occurs by external factors like infection, toxins etc. Necrosis does not contain any signaling pathway like apoptosis. It occurs when it is induced by some non-physiological disturbances (lytic viruses, hypothermia hypoxia, ischemia, metabolic poisons) without any energy provided.

3. RISK FACTORS FOR OSCC

Many factors are known that cause OSCC that results in increase the number of patients every year. There are some major risk factors that have been shown.

3.1 Chemical Factors

Tobacco-Study of several cases shows tobacco in various forms, including smoking, chewing and in betel quid etc., have carcinogenic impact on oral cavity.

Alcohol-Many cases of Oral cancer shows that alcohol is a major risk factor and also a known reason, studies have shown that individuals consuming more than 170g of whisky daily have ten times higher risk of Oral cancer than the light social drinkers. The current evidences do not suggest that pure ethanol alone is carcinogen for the development of OSCC cancer [4].

3.2 Biological Factors

Viruses-Human papilloma viruses are epitheliotropic viruses are found in the anogenital tract, urethra, skin, and larynx, tracheobronchial and oral mucosa. Frequency of HPV in oral squamous cell carcinoma and malignant potential of HPV infection has been hypothesized but not definitely confirmed.

Candida-Candida plays a role in initiation of Oral cancer. Studies have reported that nodular leukoplakia infected with candida has a tendency for higher rate of dysplasia and malignant transformation [4].

4. APOPTOTIC INDUCER

Apoptotic Incites expose pro-apoptotic consequence by means of a number of processes which included DNA cross-linking, inhibition of antiapoptotic proteins and activation of caspases. The apoptosis inducing compounds may target a specific cellular process in order to induce antitumor or antineoplastic effects. Natural compounds are able to reduce oxidative stress, which is the most likely mechanism mediating the protective effects against cancer development. In addition, *in vitro and in vivo* studies have suggested that natural compounds, such as (-)-epigallocatechin-3-gallate (EGCG), Nimbolide, Theaflavin (TF), Resveratrol and Curcumin, act by the mechanism of apoptosis.

5. NATURAL COMPOUNDS

5.1 EGCG

Green tea is a typical drink worldwide and has been read in regards to its value for wellbeing [5]. An epidemiological examination has uncovered that green tea has preventive impacts against malignancy [6]. Polyphenols in green tea incorporate numerous catechins-chiefly epigallocatechin-3-gallate (ECGG), epigallocatechin (EGC), epicatechin-3-gallate (ECG) and epicatechin (EC)- though EGCG is the most productive important polyphenol [5]. The utilization of EGCG has been presented to repress malignancy progress in vitro in creature models: the information capacity and movement or metastasis, numerous disease assortments like lung, liver, bosom, colorectal, prostate and skin cancer [7]. The quality exhibit investigation further affirmed this remarkable property of green tea polyphenols. While NHEK react to EGCG by experiencing a separation pathway [8], p21WAF1 was portion conditionally repressed on both mRNA and protein levels. Conversely, OSC2 cells, which focus on caspase 3-interceded apoptosis when presented to EGCG [9], shows raised p21WAF1 mRNA at 2 h and expanded protein levels. These perceptions propose that p21WAF1 is engaged with EGCG-initiated development capture and apoptosis in OSC2 cells; in any case, in NHEK, concealment of p21WAF1 by EGCG is related with an inhibitory instrument for caspase 3-interceded apoptosis. It's been agreeing for which green tea polyphenol EGCG contrarily controls the declaration of p21WAF1 in NHEK versus OSC2 cells; and EGCG-incited p21WAF1 is included basically in the development capture pathway just as decreased effect along caspase 3-interceded apoptosis [10].

EGCG has been proved as an inducer of apoptosis in different cell lines, e.g., HCT116, HeLa, A549, and HepG2 cells [11–12]. Various roles of EGCG with regards to apoptosis in malignant growth cells have been accounted for. An recent study proposes that EGCG increases the movement of phosphorfructokinase, causing a diminished Bcl-2 expression, which prompts expanded apoptosis in hepatocellular carcinoma

cells [13]. The affect of EGCG on apoptosis has been accounted for colon malignant growth cell line through expanded expression of p53, prompting decreased Bcl-2 protein articulation and increased Bax protein articulation [14]. It has been accounted for that the apoptotic impact of EGCG is directed by rise of oxidative anxiety in colon malignancy cells. Hindrance of ROS by N-acetyl-lcysteine (NAC), an antecedent of glutathione, can reverse the impact of EGCG-actuated apoptosis in the HT-29 cell line [15]. ROS can repress Ca2+-ATPase, prompting exhaustion of Ca2+ in the endoplasmic reticulum (ER). This exhaustion of calcium increases ER stress and triggers apoptosis [16].

In OSC2 cells p21WAF1 is involved in EGCG-induced growth arrest and apoptosis. However, in NHEK, suppression of p21WAF1 by EGCG is related with an inhibitory mechanism for caspase 3-mediated apoptosis. In the previous study it was found that Induction of p21WAF1 is a downstream event of p53 stabilization by EGCG [17].

In NHSCC cells, time and dose dependent apoptosis of EGCG has been demonstrated by Lin et al (SAS and Cal-27). Expression of Fas/CD95 induces apoptosis. In addition to increased expression of Fas/CD95, EGCG inhibits STAT3 phosphorylation, translocation to the nucleus, and leads to downregulation of the target gene products of STAT3, such as Bcl-2, Mcl-1, VEGF and cyclin D1 [18]. Thus, EGCG can induce apoptosis through effects on the mitochondria-mediated and the death receptor-mediated pathway.

Apoptosis can proceed via the mitochondria-mediated (intrinsic) pathway (including Bax, Bcl-2, and Bcl-XL proteins) and a death receptor-mediated (extrinsic) pathway (including Fas/CD95 and FADD) [19] and can be induced by agents such as drugs used for chemotherapy.

5.2 Nimbolide

Nimbolide, a terpenoid lactone followed from Azadirachta indica (neem), has different organic exercises, including cancer prevention agent, calming, antimalarial, and anticancer exercises [20]. Nimbolide has a conventional limonoid under frame with a, b-unsaturated ketones arrangement of rules and a d-lactone ringing. Its anticancereous action is alluding another, b-unsaturated ketones basic component [21]. Nimbolide as indicated by incite G0/G1 cell cycle capture, tweaks the apoptotic pathway, and increment the age of receptive oxygen species in malignant growth cells [22]. At present, nimbolide, a principle limonoid from the general neem tree (*Azadirachta indica*) joined in the posting going from ten potential characteristic mixes for OSCC treatment as per immense strip mining other than comment of solid mixes and bioactivity databases [23]. It has been explored through stream cytometry a portion subordinate increment in the sub-G1-stage populace and G2/M capture. In addition, annexin V and propidium iodide (PI) twofold recoloring uncovered an expanded extent of apoptotic cells after 24 h of nimbolide treatment [24]. What's more, 40,6-diamidino-2-phenylindole over refinement was finished so as to survey apoptosis in HONE-1 cells. Past examination has been uncovered that nimbolide causes apoptosis in NPC cell lines, recommending that it truly is an alluring chosen one for tumor treatment plans [25].

According to a recent study the inherent pathway of apoptosis prompted by nimbolide and its collaboration with the outward pathway in human bosom malignancy cell lines (MCF-7 and MDA-MB-231) [26]. The inhibitory impact of nimbolide on the development of leukemic (HL-60, U937 and THP-1) and melanoma (B16) cell lines [27] has also been explored. It has been shown that nimbolide applies antiproliferative impacts against BeWo cells by prompting apoptosis. A recent study showed that nimbolide simultaneously reverses NF-kB and Wnt flagging and initiates characteristic apoptosis in HepG2 cells [28].

Previously, it has already being studied that nimbolide induces apoptosis of HBP carcinomas by abrogating the PI3K/Akt pathway with consequent activation of GSK-3β [29]. It has already been shown that nimbolide negatively regulates activation of PI3K/Akt in oral cancer cells by inhibiting phosphorylation of Akt at Ser473 with consequent increase in p-GSK3βTyr216, the active form of GSK3β that inhibits autophagy. Nimbolide mediated ROS generation was shown to inhibit proliferation and metastasis of pancreatic cells via blockade of PI3K/AKT/mTOR/ERK signalling and activation of mitochondrial apoptosis [30].

5.3 Theaflavin-3,30 -Digallate (Tf3)

Theaflavin (TF) its derivative products, will be collectively known as theaflavins, are going to

be antioxidant polyphenols that are shaped of the condensation consisting of flavan-3-ols in tea leaves throughtout the enzymatic oxidation of black tea. Theaflavin-3'-gallate, theaflavin-3-3'-gallate, and theaflavin-3-digallate are the major theaflavins [31]. Theaflavins are varieties of thearubigins, and are therefore red in color. It has been studied that Theaflavin-3, 30 -digallate, a polyphenol in black tea, induces apoptosis in HSC-2 cell by its prooxidant action (elevation of reactive oxygen species (ROS) production) [32]. Green tea polyphenol caused apoptosis in OSCC cell line (HSC-2) in the middle of the overall gradual consisting of gene expression. The general cells redacted of caspase-3 gene didn't autonomic functions of apoptosis. This means that green tea polyphenol-caused apoptosis may be a mitochondria-targeted, caspase-3-executed steering system [33].

It has already been suggested that green tea polyphenol-inducemitochondria-targeted apotosis through, caspase-3-executed mechanism [34]. p58/KIP2 is a determinant pro-survival factor for cell protection from green tea polyphenol induced apoptosis [35].

5.4 Resveratrol

Resveratrol is a characteristic polyphenolic compound (trans-3, 4, 5-trihydroxystilbene) that is found in red grapes, berries, and peanuts and in food items got from them, for example, wine [36] and has solid enemy of inflammatory, against oxidant, cardioprotective and hostile to tumor properties [37]. Late examinations have indicated that resveratrol hinders the development of a wide assortment of tumor cells and balances numerous pathways associated with cell development hindrance, including cell-cycle capture, apoptosis, the concealment of interpretation variables, and inflammations [38]. Resveratrol treatment brought about morphological changes related with the apoptosis of OSCC cells (CAL27, SCC15 and SCC25 cell line). Hoechst recoloring exhibited that resveratrol incites a change in atomic morphology [39]. The Bcl-2 protein family assumes an essential job in the enlistment of apoptosis [40]. Bcl-2 family proteins works as to hinder and advance apoptosis; bcl-2 and bcl-xl have an enemy of apoptotic capacity; and Bax and Bak have an ace apoptotic work [41]. The job of Bcl-2 family proteins in resveratrol-initiated apoptosis was inspected utilizing Western blotch tests. Through examination it has been demonstrated that the resveratrol-incited apoptosis happens by means of the mitochondrial flagging pathway [33]. It has been discovered that resveratrol down-manages MMP, enacts Bax and Bak, restrains Bcl-2 and Bcl-XL, and discharges cytochrome c from the mitochondria [33]. Likewise, it has been demonstrated that the actuation of caspases ICAD and PARP, are related with apoptosis by resveratrol. The ongoing investigation it was exhibited that resveratrol hinders multiplication of OSCC cell lines by improving cell cycle capture in the G2/M stage and by initiating apoptosis [42].

It has additionally been indicated that resveratrol causes apoptosis by hindering the PI3K/ Akt/mTOR pathway [43,44,45,46], balancing the mitogen-enacted protein kinase pathway (MAPK) [47,48,49] and restraining NF-κB initiation [50,51]. Resveratrol activated apoptosis inside human T-cell heightened lymphoblastic leukemia MOLT-4 cells by reversing Akt phosphorylation, and hence forestalling GSK3β from being initiated [52]. Thus, resveratrol provokes apoptosis in ovarian, [53] bosom, [54] uterine, [55] prostate, [44] and different myeloma cells [56], by hindering Akt phosphorylation. Resveratrol activates apoptosis and discourages expansion of, human various myeloma cells by means of repressing the constitutive activation of NF-κB through revoking the IκB-α kinase enactment, and consequently down-controlling certain enemy of apoptotic and genius multiplication quality items, for example, survivin, cIAP-2, cyclin D1, XIAP, Bcl-xL, Bfl-1/A1, Bcl-2, and TNF-α receptor-related factor 2 (TRAF2) [56,57].

Resveratrol induce apoptosis via the mitochondrial signaling pathway. It was suggested that resveratrol down-regulates MMP, activates Bax and Bak, inhibits Bcl-2 and Bcl-XL, and releases cytochrome c from the mitochondria. In addition, to that the activation of caspases ICAD and PARP, are found to be associated with apoptosis by resveratrol. The expression levels of Apaf-1 caspase-9, caspase-3, ICAD, and PARP proteins activated and cleave caspase-3, that causes an increase in CAL27 cells. Thus, it can be suggested that resveratrol induces apoptosis via activation of the mitochondrial pathway and caspase cascades in OSCC cells [58].

5.5 Curcumin

Curcumin is a yellow shade found in the rhizome of turmeric (*Curcuma longa*) and has been

credited to different properties including, cancer prevention agent, calming, hostile to angiogenic, against proliferative and wound mending [59], without cytotoxic impacts on solid cells. It has additionally demonstrated noteworthy chemo preventive adequacy against different malignancies [60]. Different audits submit to trained that curcumin actuates apoptotic demise in malignant cells by the help of the two qualities p53-subordinate and p53-free [61,62]. The exact procedures comprising of curcumin-caused apoptosis despite everything stay not well portrayed, just as questioned characters the Bcl-2 family line and cancer prevention agent. There will be developing proof for which curcumin can cause demise in cells that is invulnerable to apoptosis [63]. As of now, treatment alongside curcumin has been expressed to actuate autophagic apoptosis in harmful cells [64]. This sort of cell passing happens without chromatin fracture, and was portrayed by the arrangement of autophagic vacuoles [65]. Curcumin shows highlights of cytotoxicity, overwhelmingly as per the general inductive thinking of mitotic calamity (MC) coldhearted mammalian cell that was among highlights of apoptosis or protein union [66]. Curcumin alone or in mix with tea polyphenols restrain the oral carcinogenesis in hamsters, conceivably by stifling the cell expansion, acceptance of apoptosis and angiogenesis [67].

Curcumin causes apoptosis in tranquil rodent thymocyte and splenocytes, human fringe blood lymphocytes, multiplying IL-2-subordinate T-cells, human leukemic (MOLT-4) cells and mouse leukemic (L1210) cells, and just in HL-60 cells old style apoptosis occurs [68].

It has also been previously analyzed that curcumin-treated OSCC cells for the presence of biochemical markers was associated with autophagy. Sudden increase of LC3-I to LC3-II conversion in curcumin-treated cells relative to control cells, proves that curcumin induces autophagy in OSCC cells. The percentage of dead cells resulting from curcumin treatment is not only attributable to apopto sis induction but also potentially autophagy when taken together. Curcumin suppresses proliferation and survival of OSCC cells through autophagic cell death. Further investigation was done to study the mechanism of curcumin induced cell death, the levels of PARP cleavage and procaspase cleavage to active caspase-3, markers of apoptotic activity, in OSCC cells. The levels of cleaved PARP and caspase-3 in response to curcumin is time-dependent [69].

5.6 Plant Extracts

5.6.1 *Imperata cylindrical*

The grass with lots of pharmaceutical and medicinal values named *Imperata cylindrical* inhibit cell proliferation and promote apoptosis in Oral squamous cell carcinoma cell line SCC-9 as in vitro model system. The methanol extract of *I. cylindrical* stimulate cytotoxicity by MTT assay. Colony forming capacity of cell line was evaluated because of clonogenic assay [70] cytometry and induction of apoptosis shown by DNA fragmentation assay [71]. The calculated value was affected by cell line and death rate of cells depends upon the treatment quantity [71]. Dose of treatment decrease the potential of cell tolerance against extract and stop the proliferation of cell cycle in G2/M phase and DNA fragmentation assay shows the death of cells because of apoptosis, which shows anticancer activity of *Imperata cylindrical* in Oral squamous cell carcinoma [71].

5.6.2 *Holarrhena antidysenterica*

A medicinal plant *Holarrhena antidysenterica* found usually in Srilanka and India and is used to treat various diseases related to stomach and intestine. It is also useful in diabetes but besides this the methanol extract of the leaves of H. antidysenterica shows an appreciable effect upon Cas9-22 gingival and HSC-3 tongue cell because of the phenolic content become toxic for reactive oxygen species, reactive oxygen species produce oxidative stress and damaged of DNA stimulus mutation and cause death of cell (apoptosis) which is useful in the treatment of oral cancer [72].

6. CONCLUSION

Carcinoma chemoprevention therapy gives an opportunity to interfere with the cancerous process and stop upcoming outbreaks. This review is focused on the apoptosis-inducing properties of several natural compounds which form an important component of the human diet and has described their beneficial effects against cancer development. These natural compounds and plant extracts play a contributing role to induce apoptosis in OSCC.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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