



Anti-carcinogenic and Anti-bacterial Properties of Selected Spices: Implications in Oral Health

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"Let food be thy medicine and medicine be thy food", as said by the father of medicine, Hippocrates in 431 B.C. Nature has provided us with a variety of treatment modalities in the form of food. For the first 5,000 years of civilization, humans relied on herbs and foods for medicine. Only in the past 60 years have we forgotten our medicinal "roots" in favor of patented medicines. While pharmaceutical ingredients have their value, we should not overlook the well-documented, non-toxic and inexpensive healing properties of food. As an individual we consume food several times a day without a complete understanding of its innate qualities. As part of a daily diet, food plays a significant role in helping our bodies function at their best. There are hundreds of extremely nutritious foods, but the items in this article do more than providing healthy nutrients. Many of them consist of ingredients with hidden pharmaceutical qualities ranging from anti-inflammatory to anti-carcinogenic agent. They not only boost our innate immunity but also act as an adjunct to medicines for specific treatment. Prevention and management of symptoms can often be improved significantly through the foods we consume regularly. This paper overviews these beneficial traits of food ingredients, consumed on a daily basis, in various oral diseases.

Key Words: Food, Medicinal plants, Mouth neoplasms, Therapeutic property

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Introduction

Oral health is responsible for social as well as physical well being of an individual. Routinely consumed food stuffs have a major impact on oral health. They are naturally bioactive and are composed of functional components like vitamins, minerals and antioxidants [1,2]. Spices and aromatic vegetables are used not only for their savor, fragrance, and appetizing effects but also for their preservative and therapeutic properties [1]. Over the past decade, a significant shift in the scientific approach with food material has lead to an alternative therapy for enhancing the well being of an individual [2,3], as naturally obtained food stuff can be consumed safely.

Food items have an array of effects such as anti-inflammatory and antibiotic properties, boosting our immune system against infections, to anti-carcinogenic properties [2,4,5]. A diet

rich in vegetables (more than 440 g/day), fruits, and spices is able to prevent at least 20% of all cancers [6]. According to a World Health Organization (WHO) report, approximately 15% of oropharyngeal cancers can be attributed to dietary deficiencies or imbalances [7]. There is a strong influence of low intake of antioxidants and fibers on oral squamous cell carcinoma in USA, Asia, and Europe [7]. Numerous studies revealed that they act as chemopreventive and chemotherapeutic agents [3]. However there is insufficient knowledge about the preventive and therapeutic aspects of these nutraceuticals in oral health care. Thus, the aim of this paper is to summarize active constituents and healing attributes of some routinely consumed spices with their mode of actions, as well as their preventive and therapeutic applications in oral health care (Table 1).

Turmeric

It is a golden herb consisting of many medicinal properties and is an effective source of treatment for various diseases since ancient times [8,9]. It is a perennial plant, known as *Circuma longa*, which is a member of the ginger family, 'Zingiberaceae'. The active constituent of turmeric is known as curcumin [10]. After consumption of curcumin, it undergoes intestinal metabolism and is absorbed, and excreted in bile [11].

Antioxidant properties

Curcumin acts as an antioxidant agent because of its phenolic structure. This compound alters serum glutathione and superperoxidase activity, reduces lipid peroxidation [10] and scavenges the reactive oxygen species. As curcumin has both prooxidant and antioxidant properties, it is a superior compound to maintain a physiological homeostasis to prevent diseases [11].

Anti-inflammatory properties

Anti-inflammatory action of curcumin occurs by lowering histamine levels and increasing the production of natural cortisone [8]. It has an anticoagulant action by preventing platelets from clumping together [8].

Anticarcinogenic properties

Most significant role of curcumin is its antitumorigenic and chemopreventive role [5]. Curcumin shows growth inhibitory effect on cell lines of various cancers like those of large intestine and bone, leukemia and oral malignant epithelium (derived from malignant tumor) [11]. In different studies on the cell lines of various cancers, curcumin inhibited proliferation of cells and accumulated cells at G2/M cell cycle [11]. A study on turmeric and oral cancer reported that curcumin taken either in diet or applied locally could significantly reduce DNA adducts [12]. The number of adducted DNA was significantly affected by 0.1% turmeric and 0.03% curcumin supplementation [13]. Most importantly, curcumin effectively repaired the broken DNA strands in the peripheral cells [14]. Curcumin also can deactivate tobacco carcinogens [8]. Pathogenesis of cancer has been associated with various proinflammatory molecules like nuclear factor Kappa (NFκ) B, interleukin (IL)-6, IL-8, and vascular endothelial growth factor (VEGF) [15]. At the molecular level curcumin suppresses tumor promoter transcription factor NFκB and apoptotic protein (AP)-1 [10]. Research demonstrated that it down-regulated the expression of NFκB, cyclooxygenase (COX)-2, and phosphorylated STAT3 in blood mononuclear cells of multiple myeloma patients [5].

Another study done by Gupta et al. [14] on inhibitory activity of curcumin on inhibitor of Kappa B Kinase (IκBK) an enzyme responsible for NFκB activation, the authors found

Table 1. Health benefits of food bioactive compounds

Food stuffs	Active ingredients	Beneficial effects
Turmeric	Curcumin	Anti-inflammatory, anticoagulant, in dental use (toothache, gingivitis, periodontitis)
Garlic	Allicin, diallyl disulfide (DADS), diallyl trisulfide (DATS)	Antibacterial, antiviral, antifungal, antiulcerogenic, anticarcinogenic
Ginger	Gingerol, paradol, zingerone	Anti-inflammatory, antiulcerogenic, antifungal, antiviral, anticlotting, in toothache
Honey	Polyphenol	Antimicrobial, antiviral, wound repair, in gingivitis, periodontitis, stomatitis, anticariogenic
Anise	1-methoxy-4-(1-propenyl) benzene	Antimicrobial, antioxidants, anti-inflammatory
Lycopene	β-carotene	Modulation of immune function, suppression of inflammation

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that there was a reduction of I κ BK activity in head and neck squamous cell carcinoma (HNSCC).

Curcumin inhibits cell signaling pathways including Akt, NF κ B, AP-1 or JNK [16]. Also curcumin up-regulates genes related to cell growth arrest and down-regulates genes related to cancer cell proliferation such as *egr-1*, *cmyc*, *bcl-X* and mutated p53. *egr-1*, *cmyc* and *bcl-X*, and abnormal tumor suppressor gene such as p53 [11]. Gene expression profiling by cDNA array was performed on total RNA extract from curcumin treated and untreated oral epithelial cancer cells. There was fourfold increase in the pro-apoptotic activating transcription factor 3 (ATF3) in the curcumin treated oral epithelial cancer cells [11]. Curcumin also effectively inhibits metastasis by decreasing invasive potential of a carcinogen through mitogen-activated protein kinase/extracellular signal-regulated kinase 3 (MEK3) and p-mitogen-activated protein kinase 12 (MAPK12: ERK3) signaling pathways which inhibit matrix metalloproteinases (MMP)-2 and MMP-9 [17]. It ceases the proliferation of endothelial cells [10] by inhibiting VEGF [17].

Curcumin has a chemopreventive effect on oral precancerous lesions like oral leukoplakia (OL) [11], oral lichen planus (OLP) and oral submucous fibrosis (OSMF) [10,18]. A study using OL lesion showed that curcumin reduced the size of a lesion by 10% in the treated 62 patients [11]. In OSMF, curcumin reduces the micronuclei formation in exfoliated mucosal cells and in circulating lymphocytes. This protective effect on micronuclei formation can help to prevent oncotransformation [10]. It can prevent and reduce the formation of fibrosis by acting as an antifibrotic agent in OSMF [9]. Its mode of action is by blocking leukocyte influx and inhibiting the activation of inflammatory cells [10].

Other therapeutic effects

Curcumin due to its inhibition on activation of inflammatory cells provides relief to patients with gingivitis and periodontitis [10]. Because of pharmaceutical effect of curcumin, it is now used as a supplement in several countries including the United States, India, Japan, Korea, Thailand, China, Turkey, South Africa, Nepal, and Pakistan [17].

Garlic

Garlic root bulb has been used for thousands of years for medicinal purposes. Allicin is an active component of garlic consisting of a high concentration of sulfur-containing amino acids, which is formed when allicin comes in contact of en-

zyme alliinase [19]. Garlic acts as an antioxidant agent because of its high content of organosulfur compounds [20].

Anticarcinogenic properties

Garlic has an important antineoplastic property. Various studies have shown that consumption of high levels of garlic decreases the risk of colon, stomach cancer and melanomas by inhibiting the growth and proliferation of cancer cells [5,19]. A previous study demonstrated that water extract of fresh garlic had apoptotic effect on cancerous cells and prevented the inception of oral carcinoma [21]. Another study using 7,12-dimethylbenz[a]anthracene (DMBA) induced buccal pouch cancer model reported that, garlic caused apoptosis of malignant cells [6]. It can act as an anticarcinogenic agent by scavenging the free radicals, increasing glutathione levels, increasing the activities of enzymes such as glutathione S-transferase and catalase, inhibiting cytochrome p450 2E1 enzyme and inducing DNA repair mechanisms; at the same time preventing chromosomal damages [5]. Thus it is an alternative therapeutic agent for primary as well as invasive cancer [21].

Other therapeutic properties

It is demonstrated that garlic plaster can be effectively used in the treatment for recurrent oral ulcers (ROU) [22]. Garlic plaster was made and applied to the oral ulcer lesions and the patients were for 1-4 years. The authors found that the complete effective rate was 83.3% while total effective rate was 100%. Garlic exerts a strong antimicrobial activity against gram-positive and gram-negative bacteria, viruses, fungi and parasites. Topical and dietary garlic has been used in the treatment of diseases like dermatologic infections and warts [19].

Ginger

Ginger is one of the most widely used condiments [1,23]. Since old ages it has been an important ingredient in Ayurvedic herbal medicines for the treatment of rheumatism, nervous diseases, gingivitis, toothache, diabetes etc. It is the rhizome of *Zingiber officinale* Roscoe of Zingiberaceae family [1]. Ginger consists of numerous pungent but active agents [1,23]. The major compound of ginger is gingerol, which can be converted to shogaols, zingerone, and paradol [1] exerting important antioxidant, anti-inflammatory, anti-cancer, anti-angiogenesis and anti-atherosclerotic pharmacological properties [24].

Antioxidant properties

Strong antioxidant activity of gingerol is due to its superoxide dismutase (SOD) like activity as it can counteract reactive oxygen species; scavenge superoxide anions, hydroxyl, peroxy and nitric oxide (NO) radicals [1,25]. Antioxidant property of ginger is used as an antiulcer therapeutic agent [23].

Anti-inflammatory properties

Ginger has a strong anti-inflammatory property by inhibiting arachidonic acid metabolism in the COX and lipoxygenase (LOX) pathways [1]. Several researches have proved that gingerdiones and shogaols can act similar to non-steroidal anti-inflammatory drugs (NSAIDs) [23]. Ginger is an effective agent against the pro-inflammatory cytokines which are secreted at the site of inflammation. It was demonstrated that ginger extract inhibited lipopolysaccharide induced activation of macrophages by inhibiting the pro-inflammatory cytokine and chemokines [26]. Furthermore, it was revealed that ginger extracts were responsible for decrease in proliferation of T cells and thus decrease in production of IL-2 and interferon (IFN)- γ . Usually macrophages act as antigen presenting cell (APC) and thus are responsible for stimulation of T cell proliferation. These activated T cells then release IL-2 and IFN- γ .

Anticarcinogenic properties

Curcumin plays a significant role in the prevention of OSMF by inhibiting myofibroblasts (MF). MFs are responsible for fibrosis by releasing transforming growth factor (TGF)- β . Curcumin inhibits the proliferation of MF and thus inhibits fibrosis. MFs are also responsible for type I and type II collagen formation which was effectively inhibited by curcumin. Curcumin is responsible for cessation of proliferation of MF by arresting the cell cycle at G0/G1 phase and increasing apoptosis [9] through a decrease in Bcl-2/Bax ratio [10]. Ginger inhibits NF κ B signaling pathway and thus represses COX-2 expressions [5]. Ginger has a dose dependent cytotoxicity on oral carcinoma cells by activating caspase-3-mediated apoptosis [25].

Other therapeutic properties

Ginger also down-regulates NF κ B-regulated gene products which reduces release of IL-8 and VEGF which are responsible for angiogenesis [24]. These favorable effects help to prevent tumor growth and metastasis [27]. Gingerols and gingerdiol has a dose dependent antimicrobial effect. Studies demonstrated that they also act as an antiviral and an antifungal agent [23,28]. It can also acts as blood thinners by inhibiting

platelet thromboxane-B2 (TBX₂) and other production [29]. These properties make it useful for the treatment of tooth ache, as a sialogogue to promote salivation for treating oral candidiasis and herpes simplex virus-1 infection [29].

Honey

Honey has both nutritional as well as medicinal value. It is composed of compounds like organic acids, proteins, amino acids, minerals, polyphenols, vitamins and aromatic compounds. Honey has antimicrobial, antiviral and antiparasitic activity.

Antimicrobial properties

Studies have proved that honey possesses strong bactericidal and bacteriostatic property. It is mainly effective against gram-positive bacteria such as *A. pyogenes*, *S. mutans*, *S. aureus* etc. Honey has shown strong antimicrobial activity because of its low water content and low pH [30]. Other than these, honey contains glucose oxidase which produces hydrogen peroxide which has a strong bactericidal action [30]. Studies demonstrate that ingestion of honey can inhibit the growth of bacteria that causes caries and thus provides a carioprotective effect [30]. It also inhibits the development of dental plaque, gingivitis, and periodontal diseases [31]. Honey has antifungal activity by inhibiting *C. albican* [30,31]. Pichichero et al. [32] studied the role of honey on *C. albicans* and found that the amylase present in honey increased the osmotic effect in the media by increasing the sugar concentration and consequently inhibited the fungal activity. Honey also shows antiviral activity against herpes labialis and rubella virus. Jungle honey acts as chemotactic inducer for neutrophils.

It also shows strong antioxidant activity by scavenging free radicals and by preventing the formation of free radicals released from the inflamed tissues [31]. Antioxidant property is due to its content of glucose oxidase, catalase, ascorbic acid, flavonoids compounds [31]. Furthermore, honey helps in increasing absorption and activity of some antioxidants like vitamin C (47%), carotene (3%), uric acid (12%), glutathione reductase (7%). The antioxidant activity is responsible for preventing several chronic diseases including cancer [30,31].

Anticarcinogenic and other therapeutic properties

Effects of tulang honey on OSCC and osteosarcoma were reported [33]. The authors demonstrated that honey has an apoptotic mechanism on OSCC and human osteogenic sarcoma (HOS) cell lines by acting as an antiproliferating agent.

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It induces apoptosis by up-regulating p53 and by modulating the expression of pro and anti-apoptotic proteins. It is also responsible for activation of caspase-3 pathway because of its phenolic and tryptophan components [29]. It was hypothesized that honey transduced the apoptotic signal via initial depletion of intracellular non-protein thiols, and then consequently reduced the MMP by increasing the ROS generation required for apoptosis [33]. Thus honey acts on cancer cell line by inducing cell-growth arrest by cell cycle blockage at the sub-G1 phase [33].

Previous studies showed that water soluble derivative of honey i.e. propolis and its associated phenolic compounds had antimetastatic effects [30,33,34]. When honey is taken orally it activates the immune system by stimulating antibodies in primary and secondary immune response. It also stimulates inflammatory cytokines production. Manuka honey (jelly type of honey) specifically increases tumor necrosis factor (TNF)- α , IL-1 β , IL-6 by stimulating monocytes. Lower immune system is more prone to cancer, thus ingestion of honey can be beneficial for immunocompromized patients [30,31]. Polyphenols like chrysin, galangin, quercetin, acacetin, kaempferol, pinocembrin, pinobanksin and apigenin present in honey has a very strong antiproliferative property [34]. Honey also has anti-ulcerogenic as well as anti-lipid effect. It has also been shown to possess anti-inflammatory, anti-atherogenic, anti-thrombotic, immune modulating and analgesic properties [31,33]. Honey is useful in preventing and controlling *S. aureus* infection by its enzymatic production of hydrogen peroxide property. Honey has a stimulatory action on wound repair and regenerative tissues [35]. Study on animal model showed that it has an ability to decrease the number of inflammatory cells and hence can act as an anti-inflammatory agent [36].

Anethole is the chief active constituent of spice fennel. Its chemical name is 1-methoxy-4-(1-propenyl) benzene [5]. Important constituent of anise is anethole dithiolethione (ADT) [37].

Antioxidant properties

ADT acts as an antioxidant agent by inhibiting lipid peroxidation and increasing intracellular glutathione and glutathione S transeferase by scavenging hydroxyl radical [38].

Antimicrobial properties

Various research on anise showed that it inhibits NO production and hence acts as a very effective antimicrobial agent.

It also inhibits lipopolysaccharide-induced NO production [38]. Anethole also acts as an antiviral agent and specifically against aciclovir-resistant herpes simplex virus-1 strains by interrupting the absorption of herpes viruses on cell wall [39]. In oral cavity, anise kills odor-causing bacteria and thus so it is a natural herbal remedy for bad breath [40].

Tomatoes

American Cancer Society recommend the guidelines for prevention of cancer. One of the key points included is that, eating five or more serving of fruits and vegetables each day can reduce the risk of cancer significantly [41]. Fruits and vegetables consist of crucial constituent as phytochemicals. They are produced by plants. They are grouped as carotenoids, isothiocyanates, glucosinolates, sulfides, diarylhepanoids, saponins [6].

Tomato is a rich source of lycopene which is a natural pigment synthesized by plants and microorganisms [42]. It is not synthesized *de novo* by the human body and hence is available from diet only. It is mostly found in human buccal mucosa and immediately enter the plasma when consumed [43]. Lycopene is an acyclic isomer of β -carotene [42]. They are found abundantly in tomatoes and in red fruits and vegetables, such as red carrots, watermelons, papayas, and grapes [43].

Anticarcinogenic properties

Non oxidative mechanism for anticarcinogenic effects of lycopene is through regulation of gap junction communication [44]. Lycopene is a significant anticancer agent by its various mechanisms. Lycopene's ability for quencher of single oxygen is twice as high as β -carotene and ten times higher than vitamin A [42,45]. It is a scavenger of free radicals preventing oxidative stress, which causes DNA damage [42,45]. Lycopene also inactivates free radicals which are responsible for lipid peroxidation process thus preventing tissue damage [42]. Another anticancer mechanism is the suppression of carcinogen-induced phosphorylation of p53, Rb antioncogenes and stopping the cell division at the G0-G1 cell cycle phase. It acts as an antiproliferative agent by inhibiting insulin like growth factor and thus reduces proliferative capacity of cells. Modulation of immune functions is carried out by regulation of intrathymic T-cell differentiation [44]. It also acts as an antitumor agent by induction of apoptosis and modulation of carcinogen metabolizing enzyme [42].

Other therapeutic effects

Various studies demonstrated that lycopene has an effect on diverse oral conditions like OSMF and OL [42]. It has been demonstrated that in OSMF, lycopene inhibited abnormal growth of human abnormal fibroblast, and an up-regulated lymphocyte resistance to stress. It has been proved that lycopene singly or with intralesional steroid injections has positive effect on mouth opening and at the same time can be helpful in alleviation of burning sensation symptoms. Thus lycopene has been claimed to be an effective, safe and reliable drug in OSMF [42].

Studies have demonstrated that it can resolve OL as they have a protective effect on cells against cell damage and progression of dysplasia [42,43,45,46], and therefore can be recommended in the treatment regimen of OL.

Conclusion

Daily consumed food has got incredible medicinal and healing properties. The healing properties of food have been reported by numerous scientific analyses worldwide [45,46]. However, the past decade has presented an outburst of clinical research to illustrate specifically what health benefits individual foods can offer, identifying the various nutrients and phytochemicals associated with these benefits. But lack of awareness and knowledge can devalue its use. Efforts to increase the understanding will help us provide a new horizon for improving various dimensions of an individuals' health. Thus prevention of disease at a household level will help improve the quality of life in the society in general.

Conflict of interest

There is no financial relationship between any author and any commercial firm(s), which may pose a potential, perceived, or real conflict of interest.

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References

1. Minaiani M, Ghannadi A, Mahzouni P, Nabi-Meibodi M. Anti-ulcerogenic effect of ginger (rhizome of *Zingiber officinale* Roscoe) hydroalcoholic extract on acetic acid-induced acute colitis in rats. *Res Pharm Sci* 2008;3:15-22.
2. McClements DJ, Decker EA, Park Y, Weiss J. Structural design principles for delivery of bioactive components in nutraceuticals and functional foods. *Crit Rev Food Sci Nutr* 2009;49:577-606.
3. Butt MS, Sultan MT. Green tea: nature's defense against malignancies. *Crit Rev Food Sci Nutr* 2009;49:463-73.
4. Zain RB. Cultural and dietary risk factors of oral cancer and precancer—a brief overview. *Oral Oncol* 2001;37:205-10.
5. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res* 2008;25:2097-116.
6. Hsu S, Singh B, Schuster G. Induction of apoptosis in oral cancer cells: agents and mechanisms for potential therapy and prevention. *Oral Oncol* 2004;40:461-73.
7. Taghavi N, Yazdi I. Type of food and risk of oral cancer. *Arch Iran Med* 2007;10:227-32.
8. Chaturvedi TP. Uses of turmeric in dentistry: an update. *Indian J Dent Res* 2009;20:107-9.
9. Zhang SS, Gong ZJ, Li WH, Wang X, Ling TY. Antifibrotic effect of curcumin in TGF- β 1-induced myofibroblasts from human oral mucosa. *Asian Pac J Cancer Prev* 2012;13:289-94.
10. Navadagi S. Gutkha in Oral Submucous fibrosis and effect of turmeric on OSMF-A histopathological study in experimental animal [dissertation]. Bangalore: Rajiv Gandhi University of Health Sciences; 2005.
11. Sharma RA, Gescher AJ, Steward WP. Curcumin: the story so far. *Eur J Cancer* 2005;41:1955-68.
12. Krishnaswamy K, Goud VK, Sesikeran B, Mukundan MA, Krishna TP. Retardation of experimental tumorigenesis and reduction in DNA adducts by turmeric and curcumin. *Nutr Cancer* 1998;30:163-6.
13. Krishnaswamy K. Traditional Indian spices and their health significance. *Asia Pac J Clin Nutr* 2008;17 Suppl 1:265-8.
14. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J* 2013;15:195-218.
15. Bielak-Zmijewska A, Koronkiewicz M, Skierski J, Piwocka K, Radziszewska E, Sikora E. Effect of curcumin on the apoptosis of rodent and human nonproliferating and proliferating lymphoid cells. *Nutr Cancer* 2000;38:131-8.
16. Lin SS, Lai KC, Hsu SC, Yang JS, Kuo CL, Lin JP, Ma YS, Wu CC, Chung JG. Curcumin inhibits the migration and invasion of human A549 lung cancer cells through the inhibition of matrix metalloproteinase-2 and -9 and Vascular Endothelial Growth Factor (VEGF). *Cancer Lett* 2009;285:127-33.
17. Gupta SC, Kismali G, Aggarwal BB. Curcumin, a component of turmeric: from farm to pharmacy. *Biofactors* 2013;39:2-13.
18. Nagabhushan M, Bhide SV. Nonmutagenicity of curcumin and its antimutagenic action versus chili and capsaicin. *Nutr Cancer* 1986;8:201-10.
19. Tattelman E. Health effects of garlic. *Am Fam Physician* 2005;72:103-6.
20. Borek C. Garlic reduces dementia and heart-disease risk. *J Nutr* 2006;136:810S-812S.
21. Balasenthil S, Rao KS, Nagini S. Garlic induces apoptosis during 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Oral Oncol* 2002;38:431-6.
22. Xie XL, Liu BJ, Yuan SH. Clinical effect of garlic plaster on recurrent oral ulcer. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2004;29:330-1.
23. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): a review of recent research. *Food Chem Toxicol* 2008;46:409-20.

24. Habib SH, Makpol S, Abdul Hamid NA, Das S, Ngah WZ, Yusof YA. Ginger extract (*Zingiber officinale*) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. *Clinics (Sao Paulo)* 2008;63:807-13.
25. Ghasemzadeh A, Jaafar HZ, Rahmat A. Antioxidant activities, total phenolics and flavonoids content in two varieties of Malaysia young ginger (*Zingiber officinale* Roscoe). *Molecules* 2010;15:4324-33.
26. Tripathi S, Bruch D, Kittur DS. Ginger extract inhibits LPS induced macrophage activation and function. *BMC Complement Altern Med* 2008;8:1.
27. Yagihashi S, Miura Y, Yagasaki K. Inhibitory effect of gingerol on the proliferation and invasion of hepatoma cells in culture. *Cytotechnology* 2008;57:129-36.
28. Kim JS, Kim Y. The inhibitory effect of natural bioactives on the growth of pathogenic bacteria. *Nutr Res Pract* 2007;1:273-8.
29. Sudarshan R, Vijayabala GS. Role of ginger in medicine and dentistry: an interesting review article. *Southeast Asian J Case Rep Rev* 2012;1:66-72.
30. Bogdanov S, Jurendic T, Sieber R, Gallmann P. Honey for nutrition and health: a review. *J Am Coll Nutr* 2008;27:677-89.
31. Othman NH. Does honey have the characteristics of natural cancer vaccine? *J Tradit Complement Med* 2012;2:276-83.
32. Pichichero E, Cicconi R, Mattei M, Muzi MG, Canini A. Acacia honey and chrysin reduce proliferation of melanoma cells through alterations in cell cycle progression. *Int J Oncol* 2010;37:973-81.
33. Ghashm AA, Othman NH, Khattak MN, Ismail NM, Saini R. Antiproliferative effect of Tualang honey on oral squamous cell carcinoma and osteosarcoma cell lines. *BMC Complement Altern Med* 2010;10:49.
34. Jaganathan SK, Mandal M. Antiproliferative effects of honey and of its polyphenols: a review. *J Biomed Biotechnol* 2009;2009:830616.
35. French VM, Cooper RA, Molan PC. The antibacterial activity of honey against coagulase-negative staphylococci. *J Antimicrob Chemother* 2005;56:228-31.
36. Cutting K. Honey and wound care: an overview [Internet]. Available from: <http://www.bee-hexagon.net/files/fileE/HealthHoney/9HoneyMedicineReview.pdf> [cited 2015]. 2015 April.
37. Chainy GB, Manna SK, Chaturvedi MM, Aggarwal BB. Anethole blocks both early and late cellular responses transduced by tumor necrosis factor: effect on NF-kappaB, AP-1, JNK, MAPKK and apoptosis. *Oncogene* 2000;19:2943-50.
38. Conforti F, Tundis R, Marrelli M, Menichini F, Statti GA, De Cindio B, Menichini F, Houghton PJ. Protective effect of *Pimpinella anisoides* ethanolic extract and its constituents on oxidative damage and its inhibition of nitric oxide in lipopolysaccharide-stimulated RAW 264.7 macrophages. *J Med Food* 2010;13:137-41.
39. Koch C, Reichling J, Kehm R, Sharaf MM, Zentgraf H, Schneele J, Schnitzler P. Efficacy of anise oil, dwarf-pine oil and chamomile oil against thymidine-kinase-positive and thymidine-kinase-negative herpesviruses. *J Pharm Pharmacol* 2008;60:1545-50.
40. Zoe C. 7 ways to be free eliminate bad breath naturally [Internet]. Available from: <http://goarticles.com/article/7-Ways-To-Be-Free-Eliminate-Bad-Breath-Naturally/3335361/> [cited 2015 January 14]. 2010 September 11.
41. Pavia M, Pileggi C, Nobile CG, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. *Am J Clin Nutr* 2006;83:1126-34.
42. Lu R, Dan H, Wu R, Meng W, Liu N, Jin X, Zhou M, Zeng X, Zhou G, Chen Q. Lycopene: features and potential significance in the oral cancer and precancerous lesions. *J Oral Pathol Med* 2011;40:361-8.
43. Singh M, Krishanappa R, Bagewadi A, Keluskar V. Efficacy of oral lycopene in the treatment of oral leukoplakia. *Oral Oncol* 2004;40:591-6.
44. Agarwal S, Rao AV. Tomato lycopene and its role in human health and chronic diseases. *CMAJ* 2000;163:739-44.
45. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. *J Natl Cancer Inst* 1999;91:317-31.
46. Maserejian NN, Giovannucci E, Rosner B, Zavras A, Joshipura K. Prospective study of fruits and vegetables and risk of oral premalignant lesions in men. *Am J Epidemiol* 2006;164:556-66.