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"THE ROLE OF XANTHINE OXIDASE INHIBITING FOODS IN THERAPEUTIC MANAGEMENT OF HYPERURICEMIA AND GOUT"

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Abstract

The state of equilibrium created between the amount of purine taken in diet, urate produced by the body itself along with the amount excreted out of the body through urine or GI tract gives out the total urate present in the body. Faulty production and excretion both can be the reason behind increased level of uric acid. Default in dietary habits has always been primary, secondary or associated cause of many ailments. Similarly in case of gout intake of purine- rich foods basically coming from animal and seafood sources can influence the development of gout. Allopurinol, is one of the potent anti-hyperuricemia drugs, being used for the treatment of gout for last many years. The mechanism of action of this drug involves the inhibition of enzyme xanthine oxidase. But long term use of allopurinol has already been associated with many side effects such nephropathy, hepatitis and many other allergic reactions. There is a need of natural anti-hyperuricemic agents.Herbs and plants that show the properties of inhibition of uric acid biosynthesis through the inhibition of xanthine oxidase can prevent hyperuricemia.In conclusion, natural antihyperuricemic agents need promotion.

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Introduction

Gout, the "unwalkable disease" as crowned by Hippocrates, is an ancient disease with unaccountable appearances in medical literature (Rymal and Rizzolo, 2014). Gout is disorder of purine metabolism, directly related to uric acid as increase in the level of uric acid which is present in form of urate in the body leads to the formation of crystals which later with time deposit as monosodium urate crystals (MSU) in tissue mainly in and around joints, causing gout. Deposition of MSU may also occur on cardiac valves. A person with serum uric acid more than 6.8mg/dL suffers from hyperuricemia, and longstanding of which is the main supporting agent in the onset of gout (Ragab et al., 2017). The state of equilibrium created between the amount of purine taken in diet, urate produced by the body itself along with the amount excreted out of the body through urine or GI tract gives out the total urate present in the body, faulty production and excretion, both can be the reason behind increased level of uric acid (Choi et al., 2005).

Xanthine Oxidase is the versatile molybdoflavoprotein enzyme from the liver which is responsible for breakdown of purine - taken in form of food, into final product- uric acid and ROS (Reactive Oxygen species). Excess formation of uric acid along with decreased excretion and deposition in the body give rise to the condition of gout. Xanthine oxidase is also one of the potent sources of superoxide radicals (Mehta and Akmal, 2014). Purine is first broken down into xanthine catalyzed by xanthine oxidase and then finally to uric acid. Purine-rich diet is highly co-related to increased plasma levels of urate and increases the incidence of gout (Jordan et al., 2007).

Defaults in the metabolism of purines due to different factors - either due to overproduction of uric acid by increased xanthine oxidase enzyme or under excretion of uric acid in urine can lead to hyperuricemia. In humans, the process of purine synthesis is largely carried out in the liver, uric acid production occurs via de novo and the salvage pathways. During the synthesis of purine nucleoside, phosphoribosyl pyrophosphate (PRPP) are formed by PRPP synthetase and then transformed into inosine 5'-monophosphate (IMP), which is then converted into either adenosine 5'-monophosphate (AMP) or guanosine 5'-monophosphate (GMP), giving out purine nucleotides. Breakdown of these nucleotides ends up into the production of uric acid.

This synthesis is catalysed by the enzyme xanthine oxidase, which converts purine into xanthine and hypoxanthine and then finally into uric acid (Moriwaki, 2014).

Gout, earlier in History has been introduced to as "the king of diseases and the disease of kings (Richette and Bardin, 2010). It is primarily divided into three stages- *Asymptomatic hyperuricemia* is the first stage of gout which is generally asymptomatic, only with increased level compared to normal level of serum uric acid. Second stage is Acute Intermittent Gout which shows onset of monoarticular joint pain with the maximum intensity in the joints. The pain disappears in few days, but can reappear within 2 years or even within shorter periods. The third stage is Chronic Tophaceous Gout or more commonly known as Chronic Gout. When acute gout is left untreated for long time it leads to enough deposition of uric acid crystals in tissues in and around joints, thus affecting other joints (Parle et al., 2013).

Prevalence of elevated levels of serum uric acid have been seen all around the world, including Philippines and Seychelles: 25%, USA: 21-22%, Japan: 20-26%, Indonesia: 18%, Russia and Nigeria: 17%, Brazil: 13%, Turkey: 12%, Taiwan: 10-52%, Thailand: 9-11%, Mexico: 11%, Sweden: 10-16%, Italy 9-12%, Iran and Saudi Arabia: 8%, China: 6-25%, Spain: 5-11% and South Korea: 5% (Smith and March, 2015). Although the prevalence of gout is increasing day by day but the public awareness about the condition is extremely poor.

Occurrence of gout is 2-6 times more common in men when compared to women and it is more prevalent during old age as 10% of men and 6% of women more than 80 years old of the common population suffer from it. Poor dietary intake, decreased physical activities, obesity and metabolic syndromes etc aid in increasing the incidences (Ragab et al., 2017).

Rapid growth of morbidity and trend in young people all around the world, in the recent years has shifted focus on the ill effects of hyperuricemia. Allopurinol, is the only potent anti-hyperuricemia drug, that is being used for the treatment of gout for last many years. The mechanism of action of this drug involves competitive inhibition of enzyme xanthine oxidase. But long term use of alloupurinol has already been associated with many side effects such

nephropathy, hepatitis and many other allergic reactions (Azzawie and A.Abd, 2015). We therefore need natural alternative of hyperuricemia drugs.

Default in dietary habits has always been primary, secondary or associated cause of many ailments. Similarly in case of gout intake of purine- rich foods basically coming from animal and seafood sources can influence the development of gout. Avoiding or reducing amount of purine-rich foods intake, especially of animal origin, may help reduce the risk of gout attacks. There are abundant types of gifted spices and herbs, cultivated all around the world, with magical properties. From ancient times plants and there parts have been traditionally used in treatment of many diseases, hyperuricemia being one of them. Therefore, use of many herbs and plants showing the properties of inhibition of uric acid biosynthesis through the inhibition of xanthine oxidase can prevent hyperuricemia.

Black Pepper (Piper nigrum)

Black pepper is one of the most common spices used in kitchen and is considered as the "King of Spices ". It is from the family of Piperaceae, native to India, most part being its fruit. It i dried and then used as a spice or in seasoning. It is not only used for taste but also has its aura in the field of medicinal treatment (Srinivasan, 2007).

The most important active compound of black pepper is piperine. Piperine is not only braced with a number of effective properties against many disease and ailments but also has bio-enhancing effects on many therapeutic drugs. Black pepper posses the properties of being anti diabetic, anti-bacterial, anti-depressant, anti-fungal, anti-oxidant, anti-inflammatory, anti-pyretic, anti-tumor, anti-thyroid, hepato-protective and many more(Ahmad et al.,2012).

Black pepper also has shown its capacity to inhibit xanthine oxidase activity. Black pepper showed high xanthine oxidase inhibition that was up to 70.9% (Dziki, 2012).Piperine was also found useful in reducing the inflammation caused due to monosodium urate crystal deposition (Sabina et al., 2014).

Betel (Piper betle)

Betel or "Piper betle", is a vine plant that comes from the family of pepper and kava – Piperaceae.It is mostly cultivated in Southeast Asia, as leaves of betel is consumed largely in form of "Paan" in India. The practice of chewing "paan" goes back to 400 BC. There are evidences of use of betel leaves even in literatures from Ayurveda, Charaka, Sushruta Samhitas, and Kashyapa Bhojanakalpa (Toprani and Patel, 2013).

Allylpyrocatechol, hydroxychavicol, piperbetol, ethylpiperbetol, piperol A, piperol B, chavibetol, and alkaloids are the main active constituents present in betel which account for its beneficial medicinal activities (Haslan et al.,2015).These active constituents impart them the advantage of being analgesic, anti-bacterial, antioxidant, antiseptic, cardiotonic, digestive, diuretic, laxative, hepatotonic etc (Duke et al.,2002).

The enzyme hydroxychavicol present in betel can be credited for its inhibitory effect against xanthine oxidase (Shaffer, 2014). There are evidences from many researches that aid the fact that betel leaves can serve as a potent source for inhibition of xanthine oxidase, the main enzyme that converts purine into uric acid, and even pointing out that hydroxychavicol is more effective than the common anti -hyperuricemia medicine, allopurinol (Murata et al.,2009).

Turmeric (Curcuma *longa* L.)

Turmeric, from the family of Zingiberaceae , is the "Golden spice of India" , with its numberless medicinal worth, it has been used in India for ages, from about 4000 years back during the Vedic culture. Only on the basis of its miraculous effect and wide range of medicinal benefits, this herb has shown its magic all around the globe. From its use in the daily kitchen routine to day to day use in many ailments, it has vast scope as a treating agent of many diseases (Chattopadhyay et al., 2004).

Turmeric basically hails from South-East Asia; it is used as a coloring agent and preservative with no known side effects in most of the Asian countries like India, China, Bangladesh, Bhutan etc (Rathaur et al., 2012). If facts are to be believed India is the largest producer of turmeric all over the world (Deepa, 2007). Turmeric comprises of protein (6.3%), fat (5.1%), minerals

(3.5%), carbohydrates (69.4%) and essential oil (5-8%) - α-phellanderene (1%), sabiene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%) (Tohda et al., 2006). The most essential curcuminoid of turmeric is curcumin, which was isolated for the first time in 1815. 2-5% of turmeric was estimated to be curcumin. Turmeric possess the properties of being analgesic, antibacterial, anti-microbial, anti-inflammatory, antioxidant, antiulcer, anti-cancer, cardio-protective, gastro-protective and many more to count (Duke et al.,2002).

Turmeric due to the presence of curcumin holds effective place in the treatment of gout as it reduces the effect of xanthine oxidase, the primary enzyme responsible for uric acid production. Xanthine oxidase is binded weakly by curcumin and further its products from the degradation show effective inhibition action against xanthine oxidase.The effect of turmeric on inhibition of Xanthine oxidase is basically due to the inhibitory action of curcumin by directy inactivating at the protein level and by reducing the conversion of xanthine dehydrogenase (XD) to xanthine oxidase (XO) (Lin and Shih,1994; Shen and Ji, 2009).

Onion (Allium cepa L.)

Onion is one of the most easily found and common condiment used as a cooking ingredients in India. It belongs to the Alliaceae family and is a biennial herb (Zubair et al., 2009). It is one of the oldest used herbs with edible leaves and bulbs. Onion represents the shape of bulb, thus, is often also termed as bulb onion (Sohail et al., 2011).

There are proofs of presence of carbohydrates (11.6%), Moisture (86.8%), protein (1.2%), fat(0.1%), calcium (0.2-0.5%), phosphorous (0.05%), and traces of aluminium, iron, copper, zinc, manganese along with Vitamin A, B_1,B_2, C, nicotinic acid and pantothenic acid fresh in fresh onions. Onion is a also a rich source of many flavonoids, polyphenols, saponins and especially organic sulphur such as allyl propyl disulfide, dipropyl disulfide, methyl propyl disulfide and their trisulfides (Rabinowitch and Brewster, 1990).

Onion also has its role in many diseases such as anti-bacterial, anti- depressant, hepatoprotective, anti- diabetic, cardioprotective, hypolipidemic, anti cancer, anti- pathogenii etc due to its vast

medicinal values because of the presence of rich amount of flavonoids, polyphenols, saponins and organic sulphurs (Duke et al.,2002; Sohail et al.,2011).

The presence of polyphenols are responsible for the anti gout property of onion which is through inhibiting the xanthine oxidase activity, the main responsible authority for onset of gout. Onion showed to decrease the levels of uric acid in artificially induced hyperuricemic rats, showing their potential of lowering uric acid (Haidari et al., 2008).

Tea Plant (Camellia sinensis)

Camellia sinensis, is a cash crop grown mostly in parts of South east Asia and China. It is a evergreen shrub, which is being consumed by humans for uncountable years After water, Tea has been talked about as the most enriched and consumed beverage in the world (Jiang et al., 2015).Its medicinal benefits have been talked about for about over 5000 years. Tea contains riboflavin, folic acid, β-carotene, α-tocopherol and phylloquinone etc. The ill after-effects of caffeine by interaction with polyphenols is altered, and thus it can be lured without worrying about the after effects (Stagg and Millin, 1975).

The presence of many polyphenols (catechins and flavonoides), alkaloids (caffeine, theobromine, theophylline, etc.), volatile oils, polysaccharides, amino acids, lipids, vitamins (e.g., vitamin C), inorganic elements (e.g., aluminium, fluorine and manganese)etc, braces it with many medicinal properties such as, antioxidant, anti- cancerous, cardioprotective, anti-diabetic, anti-inflammatory, digestive, hepatoprotective, immunity booster etc (Sharangi, 2009).

Active compounds - catechin, epicatechin ,epigallocatechin,epicatechin gallate and epigallocatechin gallate, which are present in tea have been accounted for their role in inhibition of xanthine oxidase activities. They not only act on the produced reactive oxygen species but also hinder their production by acting actively (Aucamp et al., 1997). There are evidences of both black tea and green tea being effective in gout, black tea being comparatively more effective (Zhu et al., 2017).

Apple (Malus pumila) Apples are among the largely eaten fruits in countries all over the world, the edible and sweet fruit of Malus pumila (apple tree), a deciduous tree, is native to Central Asia and Europe. They can be eaten fresh or in form of juices and dried apple .Apples are rich in polyphenols and flavonoids such as quercetin, catechin, phloridzin and chlorogenic acid etc which impart it with properties like antioxidant, anti-inflammatory, blood pressure reduction, anti-cancer, weight loss, anti-diabetic etc (Boyer and Liu, 2004; Ferretti et al.,2014).

When the calibre of apple was compared to that of allopurinol- the medicine for gout treatment, it was seen that apple has the potential of inhibiting the xanthine oxidase activity, thus lowering uric acid levels. This was because of the presence of polyphenols which helped in lowering vascular oxidative stress and reducing uric acid (Cicero et al., 2017).The polyphenols present in apple inhibited xanthine oxidase through anti-competitive mode, thus showing more effectiveness (Shi et al., 2014).

Ginger (Zingiber officinale R.)

Apart from garlic, turmeric and other condiments ginger is also widely consumed and used kitchen food item all over the world. Ginger is from the family of cardamom and turmeric-Zingiberaceae, but there are no information regarding its actual origin, since it does not grow in wild. The rhizome of ginger (Zingiber officinale R.), commonly known as " Adrak", in hindi, is the most consumed part (Benzie and Galor, 2011).

Fresh ginger contains gingerol as the major compound, along with other 115 identified compounds (Jolad et al.,2005).Other phytochemicals include zingerone, shogaols, gingerols, pardols, β- phellandrene, curcumene,cineole, geranyl acetate, terphineol, terpenes, borneol, geraniol, limonene, β- elemene, zingiberol, linalool, αa-zingiberene, β-sesquiphellandrene, β-bisabolene, zingiberenol and α-farmesene which aid to its medicinal and therapeutic values (Ali et al.,2008). Presence of these many phyto-constituents adds on many properties such as anti-microbial, antiviral, gastro-protective, anti-diabetic, anti hypertensive, cardio-protective, anticancer, chemo-preventive, analgesic, anti-allergic, anti-aggregant, anticonvulsant, antidepressant, anti-edemic, anti-inflammatory, anti-lipidemic, antipyretic, hypotensive, anti-neoplastic etc (Duke et al.,2002).

Ginger along with the above properties, also possess the art of being anti- hyperuricemia, as according to a research carried out on rats showed that intake of ginger lowered the uric acid levels in hyperuricemic rats but not in rats with normal uric acid levels, while, allopurinol reduced blood uric acid levels of rats with high blood uric acid levels as well as with normal ones too, even lower than the normal range, suggesting that in treatment of hyperuricemia, ginger will have lesser side effects when seen with allopurinol. This effect of ginger can be because of the presence of flavonoids, which inhibit the activities of enzyme that is responsible for uric acid overproduction i.e., xanthine oxidase (Owen and Johns, 1999; Azzawie and A.Abd, 2015).

Olive (Olea europaea)

Olea *europaea*, the botanical name for Olive tree, is from the family of Oleaceae.The fruit of Olea europaea, also known as olive, is the most used part of this small tree. It is mainly found warm and tropical areas of the world, mainly the Mediterranean region along with areas of south eastern Europe, western Asia and northern Africa. 98% of the world's total olive production comes from the Mediterranean region only (Parvaiz et al., 2013).

The olive fruit contains phenolic compounds including phenol acids- vanillic acid, gallic acid, caffeic acid,ferulic acid and sinapic acid, phenolic alcohols- oleuropein, orhydroxytyrosol and p-hydroxyphenylethanol (tyrosol), and flavonoids- luteolin 7-O-glucoside, rutin, apigenin 7-O-glucoside, anthocyanins, cyanidin 3-O-glucoside and cyanidin 3-O-rutinoside (Dekdouk et al., 2015). While the olive oil comprises of monounsaturated fatty acids (MUFAs) -oleic acid' and important minor components including aliphatic and triterpenic alcohols, sterols -sitosterol, hydrocarbons -squalene, volatile compounds, tocopherols, pigments such as chlorophylls, carotenoids, -carotene, β-carotene, lutein and antioxidants (Andrikopoulos et al.,2002).

During a research, when Mediterranean diet was enriched with virgin olive oil, it was seen that the antioxidant powers of it was increased while it also reduced the activities xanthine oxidase enzyme (Sureda et al.,2016).Extracts of Virgin olive oil showed the inhibition of xanthine oxidase by 73%, while refined virgin oil showed 48% of inhibition (Steinkopff, 2002). Leaves of olives also posess the ability to decrease uric acid levels. The presence of polyphenolic compounds -oleuropein, caffeic acid,luteolin-7-O-β-D-glucoside and luteolin can be given as the

reason behind Olive leaf's inhibitory effects on xanthine oxidase (Flemmig, et al.,2011).Thus, confirming the role of olives in treatment of hyperuricemia.

Celery (Apium graveolens)

Celery is most commonly known as "Dhaniya", in Indian regions, is a medicinal herb plant from the family of Apiaceae. It is grown commercially in parts of Europe and the tropical and subtropical regions of Africa and Asia. India grows approximately 40 000 tons per year of celery and exports 250 tons of it. The seeds, leaves and essential oils of celery are the most used parts of it, whether in cooking or in traditional treatment of different ailments (Kooti and Daraei, 2017).

The curative effect of celery is basically due to the presence of its magical active constituents such as - limonene, selinene, frocoumarin glycosides, apigenin, luteolin, kaempferol and vitamins A and C etc (Kooti et al., 2015). Celery can be used in treatment of many diseases since it has anti cancer, anti-diabetic, analgesic, antiarthritic, antidepressant, anti-inflammatory, antiseptic, anti-oxidant, anti-tumor, anti-bacterial, diuretic, hypoprotective, uterotonic etc (Duke et al.,2002).

Oral administration of celery in 36 male albino rats induced with gout, showed to lower malonaldehyde (MDA) levels and upgrade antioxidant enzyme activities, showing that celery is a beneficial herb in treatment of gout (Abd El-Rahman and Abd–ELHak, 2015).It was also seen that xanthine oxidase enzyme activities are hindered by all the extracts of celery, this can be credited to the presence of flavonoid - apigenin via competitive inhibition, along with luteolin, kaempferol being potent inhibitors (Iswantini et al., 2012).

Conclusion

Gout is disorder of purine metabolism, directly related to uric acid being its end product. Increase in the level of uric acid which is present in form of urate in the body leads to the formation of crystals which later with time deposit as monosodium urate crystals (MSU) in tissue mainly in and around joints, causing gout. Defaults in the metabolism of purines due to different factors - either due to overproduction of uric acid by increased xanthine oxidase enzyme or under

excretion of uric acid in urine can lead to hyperuricemia or even gout. There are abundant types of gifted spices and herbs, cultivated all around the world, with magical properties. From ancient times plants and there parts have been used, traditionally, in treatment of many diseases, hyperuricemia being one of them. Therefore, many natural herbs and plants that show the properties of xanthine oxidase inhibition provide safe and effective alternative to allopathic drug.

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