Quercetin- herbal bioactive nanotechnology for osteoarthritis & elderly health

Quercetina - nanotecnologia bioativa herbal para osteoartrite e saúde do idoso

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ABSTRACT
Quercetin is rapidly emerging “bioactive” in the western world in the form of food supplement or healthy ingredient to address several lifestyle issues such as cardiovascular, hypertension and diabetes issues, obesity and cancer. It is a flavanoid found common in some healthy fruits and vegetables/spices such as Red Onion, Coriander, Pomegranate, Asparagus, Green Tea, Coffee etc. It is highly anti-inflammatory and sold as over the counter food supplement in the western world to address cardiovascular, hypertension and diabetes issues. Osteoarthritis, an auto-immune disease prevails among the musco-skeletal diseases that comprise 4th most disabling conditions among elders globally but no proven drug yet (Shen et al., Quercetin has shown to attenuate it in vivo, in vitro and even limited human trials by scavenging free radicals that and preventing the loss of bone/cartilage/muscle. However, quercetin bioabsorption is low so we propose its conjugation with non-polar amino acid viz. Glycine for multiplier effect. Glycine is a key component of Glutathione, the natural antioxidant in the human body. Glycine alone shown to improve collagen synthesis by articular chondrocytes in vitro and its deficiency may cause osteoarthritis, vide literature. So its conjugate with Quercetin boost the Glutathione level & improve body’s own antioxidant system, to reduce the cartilage loss and prevent osteoarthritis.

Keywords: phytochemical, antioxidant, polyphenol, bone, cartilage.

RESUMO
A quercetina está emergindo rapidamente como "bioativo" no mundo ocidental na forma de suplemento alimentar ou ingrediente saudável para tratar de vários problemas de estilo de vida, como problemas cardiovasculares, de hipertensão e diabetes, obesidade e câncer. É um flavanoid encontrado comumente em algumas frutas e legumes/especiarias
saudáveis, como cebola vermelha, coentro, romã, aspargos, chá verde, café etc. É altamente anti-inflamatório e vendido como suplemento alimentar de venda livre no mundo ocidental para tratar de problemas cardiovasculares, hipertensão e diabetes. A osteoartrite, uma doença autoimune, prevalece entre as doenças musculosqueléticas que compreendem a quarta condição mais incapacitante entre os idosos em todo o mundo, mas ainda não há medicamento comprovado (Shen et al. A quercetina demonstrou atenuá-la in vivo, in vitro e até mesmo em testes limitados em humanos, eliminando os radicais livres e evitando a perda de osso/cartilagem/músculo. No entanto, a bioabsorção da quercetina é baixa, por isso propomos sua conjugação com um aminoácido não polar, a glicina, para obter um efeito multiplicador. A glicina é um componente essencial da glutatonia, o antioxidante natural do corpo humano. A glicina sozinha demonstrou melhorar a síntese de colágeno pelos condrócitos articulares in vitro e sua deficiência pode causar osteoartrite, vide literatura. Portanto, seu conjugado com a quercetina aumenta o nível de glutatonia e melhora o sistema antioxidante do próprio corpo, para reduzir a perda de cartilagem e prevenir a osteoartrite.

Palavras-chave: fitoquímico, antioxidante, polifenol, osso, cartilagem.

1 INTRODUCTION

Medicinal plants- Herbal trade is growing rapidly worldwide as safer, long term therapy given the adverse drug reaction (ADR) that haunts the medical, chemical medicine under allopathy and is speculated to reach $5 trillion by 2050 (WHO, 2009, Greenwell & Rahman, 2015). Growing anti-microbial resistance (AMR) to the modern medicine extant molecules is another major and new driver for this trend as medicinal plants are used for millennia effectively (Anand, 2019). Herbal remedies are considered effective and becoming popular in addressing chronic, lifestyle ailments such as diabetes, blood pressure and heart ailments such that even in the USA, about a quarter of the population have used herbal medicine sometimes (Ghate & Wele, 2021). Several medicinal plants are commonly used to treat arthritis globally such as Guggulu/ Indian Myrrh (Commiphora wightii), Indian frankincense (Boswellia serrata), Hadjod/ Veld Grape (Cissus quadrangularis), Drumstick (Moringa olifera), Turmeric (Curcuma longa) and overharvest has led to the extinction threat to the first 3 species & need substitution by cultivated species to conserve biodiversity & avoid resource scarcity/ adulteration (Ghate et al, 2022).

Osteoarthritis- Knee/ hip joint arthritis is an auto-immune disease prevails among the musco-skeletal diseases that comprise 4th most disabling conditions among elders globally but without gold standard remedy yet (Singh et al, 2022, Woolf, 2015). Ayurvedic medicine is shown to be effective in treating even Rheumatoid Arthritis, more
complex health condition in clinical trials in Europe (Furst et al, 2011, Kessler et al, 2018). However, while traditional medicine focuses on formulations of plants part or their extracts or combinations but the modern medicine has focussed on extraction & development of “active ingredients” i.e. phytochemicals as it is easy to patent such discrete objects (Patwardhan et al, 2004, Vaidya, 2007). Aspirin, Morphine, Menthol etc. are super-molecules that emerged as multi-billion dollar industry in the past century (Schmidt, 2008). Aggressive phytochemicals such as Alkaloids emerged as “star-drugs” then but 21st century is witnessing emergence of mild bioactives viz. polyphenols such as with subtle, tacit effects (Del bo et al, 2019).

Curcumin- A recent global hit molecule emerging in the past decade, is “curcumin” obtained from the famous Indian spice Turmeric (Agarwal et al, 2011). It is promoted globally today as the smoothie “Turmeric latte” as anticancer, anti-inflammatory health supplement, an over the counter (OTC) product. However, its bioavailability is low like other flavonoids (a type of polyphenol), so huge, amounts need to be consumed for medicinal effect which is unfeasible (Anand et al, 2007). In fact, curcumin alone is found to be effective treatment for osteoarthritis (Henrotin et al, 2013). However, some people experience adverse effects such as stomach upset, nausea, dizziness, diarrhoea (Sharma et al, 2004). For, it is Turmeric is considered as having “hot” potency as per vide traditional knowledge now documented in India under People’s biodiversity Register (Utkarsh, 1999, Ghate, 2001). As per own practical experience, Turmeric excess consumption causes side effects such as pimples, boils, blood letting in stool/ piles indicating the body heat it generates. Hence, it is advised in traditional medicinal systems such as Ayurveda, to be consumed with milk, a coolant for a balanced effect. Further, polyphenols such as Curcumin, a flavonoid, are not water soluble but are lipid soluble so fat content in the milk enhances its bio-absorption (Bali et al, 2022). Combination in with the alkaloid such as Piperine improves its bioavailability by 8 times (Kesarwani & Gupta, 2013) as was done by traditional boiled milk drink with Tuemeric & Black pepper in Ayurveda. Curcumin is an organic molecule, is not water soluble, and is better absorbed in fat medium such as milk or butter/ Ghee (clarified butter). Turmeric water decoction is also promoted as health drink globally but low bioavailability may constrain its benefits so it may be wrong recipe. There is thus need for a safe herbal drug and we explore the role and scope of Quercetin in this context here. Inflammation is the main physiological explanation to majority of the non communicable, chronic diseases so we explored the relative anti-inflammatory potential of quercetin and few other
promising ingredients from spices, which are considered “grandma’s herbal kit” and contain very powerful bioactive ingredients (Ghate & Kulkarni, 2023a).

Quercetin- A promising therapeutic molecule rapidly emerging recently is Quercetin, a flavonoid, found highly anti-inflammatory and potential and safe cure for many lifestyle diseases (Victor et al, 2016). It is sold today as over the counter food or health supplement in the western world to lessen the intensity of many lifestyle ailments such as cancer, cardiovascular, hypertension and diabetes (Salehi et al, 2020). It is found common in some healthy fruits and vegetables/spices such as Red Onion, Coriander, Red Grapes, Okra, Pomegranate, Tea, Coffee, Asparagus, Ashwagandha {Indian Ginseng-Withania somnifera (L.) Dunal} etc. Quercetin has shown promising results to attenuate Osteoarthritis (Salehi et al, 2020) in vitro, in vivo (Li et al, 2021) and even limited human trials on rheumatism (Javadi et al, 2017). For, Quercetin may be useful in treating very challenging auto-immune diseases it has been shown (Shen et al, 2021). The availability of Quercetin in some common diet items is depicted in table 1 for instance-

<table>
<thead>
<tr>
<th>Source</th>
<th>Quercetin mg/100 g fresh weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td></td>
</tr>
<tr>
<td>1. Apples</td>
<td>4.01</td>
</tr>
<tr>
<td>2. Asparagus</td>
<td>14.0</td>
</tr>
<tr>
<td>3. Broccoli</td>
<td>13.7</td>
</tr>
<tr>
<td>4. Chili pepper</td>
<td>32.6</td>
</tr>
<tr>
<td>5. Kale</td>
<td>22.6</td>
</tr>
<tr>
<td>6. Lettuce</td>
<td>14.7</td>
</tr>
<tr>
<td>7. Onions</td>
<td>45.0</td>
</tr>
<tr>
<td>8. Spinach</td>
<td>27.2</td>
</tr>
<tr>
<td>9. Chives</td>
<td>10.4</td>
</tr>
<tr>
<td>10. Dill</td>
<td>79.0</td>
</tr>
<tr>
<td>11. Fennel leaves</td>
<td>46.8</td>
</tr>
<tr>
<td>12. Oregano</td>
<td>42.0</td>
</tr>
<tr>
<td>13. Blueberry</td>
<td>14.6</td>
</tr>
<tr>
<td>14. Cherry</td>
<td>17.4</td>
</tr>
<tr>
<td>15. Cranberry</td>
<td>25.0</td>
</tr>
<tr>
<td>AVERAGE</td>
<td>28</td>
</tr>
<tr>
<td>Beverage</td>
<td>mg/100 ml</td>
</tr>
<tr>
<td>Black tea</td>
<td>2.50</td>
</tr>
<tr>
<td>Red wine</td>
<td>3.16</td>
</tr>
</tbody>
</table>

Source: Dabeek and Marra (2019)
#estimated from lee et al (2016) to contain 4 mg in 1 teaspoon powder (2 g) as 100 mg coffee bean are said to contain 200 mg Quercetin, which is 5 times the Caffeine quantity. Daily 3 cups imply 10-12 mg quercetin consumption.

## 2 MATERIALS & METHODS

As inflammation is found as the underlying cause behind many chronic ailments (Aggarwal et al, 2011), we assessed the anti-inflammatory potential of bioactive compounds in major spices in India through docking study performed at Rasa Life. Co., (www.rasalsi.com, Ghat & Kulkarni, 2021). Their potential was assessed against COX2 (cyclooxygenase) the chief mediator of inflammation (Chen, 2010) using active site PDB ID 5IKR obtained from PDBsum (Laskowski et al, 2018). We also consulted literature.

## 3 RESULTS

We found Quercetin to be 2nd most potent bioactive ingredient after Piperine, an alkaloid super-molecule and both surpassed Curcumin the current wonder-drug being famous globally, as shown in table 2.

<table>
<thead>
<tr>
<th>SPICE</th>
<th>Bioactive ingredient</th>
<th>Docking score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Pepper</td>
<td>Piperine</td>
<td>-9.99</td>
</tr>
<tr>
<td>Coriander</td>
<td>Quercetin</td>
<td>-9.94</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Curcumin</td>
<td>-8.66</td>
</tr>
<tr>
<td>Ginger</td>
<td>Gingerol, Shogaol</td>
<td>-7.34-7.51</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Diosgenin</td>
<td>-6.8</td>
</tr>
<tr>
<td>Clove</td>
<td>Eugenol</td>
<td>-6.66</td>
</tr>
</tbody>
</table>

Source: Ghat & Kulkarni, 2021.

We estimate quercetin content in typical Indian diet using data & method of Singh et al (2015) and data on Indian spice consumption from Ferucci et al. (2010). Indian diet is said to be effective in maintaining immunity and health of the elderly due to spices & polyphenols (Kulkarni & Ghat, 2023).

<table>
<thead>
<tr>
<th>FOOD ITEM</th>
<th>QUERCETIN CONTENT mg/100 g</th>
<th>Diet g/day</th>
<th>Quercetin content mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onion</td>
<td>45</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Coriander*</td>
<td>45</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Chilli</td>
<td>32</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Tea/ coffee</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Okra*</td>
<td>30</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Spinach*</td>
<td>27</td>
<td>5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 3- Quercetin consumption daily estimate in average Indian diet
4 DISCUSSION

Immunity- Indians may be consuming about 20 g Quercetin daily on average which is similar to the world famous Oriental i.e. Japanese diet -17 mg/ day (Nishimuro et al, 2015) and another healthy diet famous globally viz. Mediterranean diet (Dilis V and Trichopoulou, 2010). Thus, it is argued that Indian diet to is as healthy as the 2 and called as “indo-Mediterranean” diet to popularize it easily (Singh et al 2022 b). Indian Quercetin consumption levels may be 4-5 times that in than USA from the above data where only 3-5 mg/ daily Quercetin consumption from diet is mentioned (Dabeek & Marra, 2019). Thus, it is thus widely sold as health supplement in USA for instance (Salehi, 2020). But since it is not water soluble and is lipid soluble, its bioabsorption and effectiveness may be suboptimal as said before.

This explains the 10 times less prevalence & mortality of COVID-19 in India per 100,000 population (0.8 % and 1.2% respectively- the mortality rate is the % of the COVID-19 patients dying) than USA or EU in the 1st year, pre-vaccine phase of the pandemic (Ghate & Kulkarni, 2021). Plant based diet is found to build immunity and reduced risk of even pandemics such as COVID-19 based on negative correlation between the 2 as observed across European nations (Ghate & Kulkarni, 2023). Of course, Quercetin is not the only dietary ingredient responsible for better health of (adult) Indians, per capita flavonoid consumption here is among the highest in the world (1,800 mg/day, Singh et al, 2022 b) compared to 1,500 mg/day in japan & strictly Mediterranean (250-400 mg/day) or other European countries (350-900 mg/day) and much higher than the USA (132 mg/ day). In fact, lower 4 times cancer incidence in India (Bray et al, 2018) may be related to its higher spice consumption (Ferucci et al, 2010), its postulated (Ghate& Kulkarni, 2021, Aggarwal et al, 2011).

The authors attributed it to the higher immunity caused by spicy Indian diet rich in polyphenols, the healthy phytochemicals, that boost immunity. They also mentioned much lower level of immunity compromising food consumption in India such as meat, liquor and Tobacco. Later, they added that the prevalence of packed foods abroad in the western Countries that contains preservatives and potentially carcinogenic or unhealthy ingredients to be immunity buster (Ghate and Kulkarni, 2023). For, in India people

<table>
<thead>
<tr>
<th>Apple</th>
<th>4</th>
<th>25</th>
<th>1</th>
<th>17.2</th>
</tr>
</thead>
</table>

* These are also known to be rich in Quercetin like Onion but less than it.
Source: own estimate
mostly eat home cooked food and little packed food or hoteling is done thus reducing the extent of unhealthy chemicals consumption.

Quercetin being among the to-antioxidant, anti-inflammatory bioactive was found in parallel in the studies in Russia (Manukyan et al, 2020) and Saudi Arabia (Shazi et al, 2020). The values are also higher than the synthetically designed ‘best’ molecule- i.e. 4-(4-methyl-1-piperazinyl)-2-phenyl[1]benzofuro[3,2-d] pyrimidine discovered in the Saudi Arabia (ibid.) or isatin (benzohydrazide) (Ravi et al, 2016). Quercetin scavenges the free radicals that damage the tissue and thus preventing the bone/ cartilage/ muscle loss occurring in osteoarthritis oxidation by reactive Oxygen Species (ROS). Quercetin is power biomolecule that even inhibits the metabolic effect of caffeine (Xiao, 2014 ) which his considered as among the strongest of dietary bioactive/ medicine so prohibited during homeopathic medication.

Quercetin is not yet established as proven drug through large scale or multi-country trials and the results so far are limited to pre-clinical trials or say hundred patients in lieu of disease other than osteoarthritis (Salehi et al, 2020). It is found effective even to treat COVID-19 if jointly administered with adjuvant such has vitamin C (Manuel et al, 2020). It is also found senolytic and being tested for anti-aging effect along with Dasatinib (Cavalcante et al, 2020). Senolytics are a class of drugs that selectively clear senescent cells (SC). The first senolytic drugs include Dasatinib, Quercetin, Fisetin and Navitoclax.

Pharmacokinetics- Table 2 implies that if one consumes 50-100 gram fresh weight of above vegetables daily and/ or 3-4 cups of tea/ coffee/ wine, their Quercetin consumption can be 10-15 mg/day. Equal consumption from fruits/ vegetables/ spices can be additional to it, totalling 25-30 mg/ day. The above study mentions that clinically effective dose recommendation is 500 mg/ day i.e. 30 times the average daily intake. Traditional medicine systems such as “Ayurveda” facilitated it by hyper-boiled decoction of polyphenol rich herbs in lipids called as “Asava/Arishta”or active carbon compounds termed as “Bhasma” (Pal et al, 2014). It was historical nanotechnology.

Interestingly, positive effects of Quercetin diet were observed at lower dose also-150 mg/ day i.e. 30% of the clinically prescribed level above in addressing the hypertension and its consumption is safe upto 945 mg/ day/ head (Victor et al, 2016). In toxic dose, quercetin caused emesis, hypertension, nephrotoxicity, and reduction in serum potassium. They quoted distribution and elimination half-life of intravenous quercetin is 0.7–7.8 min, and 3.8–86 min, respectively. The clearance is 0.23–0.84 L/min/m², and
volume of distribution is 3.7 L/m$^2$ (Ferry et al, 1996). Erlund et al. studied the pharmacokinetic properties of 8, 20, and 500 mg quercetin aglycone orally in healthy volunteers (Erlund et al, 2000). Graefe et al. (2001) also studied pharmacokinetic properties of quercetin at the dose levels of 200 mg. C$\text{max}$ and T$\text{max}$ of quercetin are 2.3 ± 1.5 µg/mL and 0.7 ± 0.3 h, respectively. Further, its aglycone form if more effective and prevalent than its other forms that are also gaining popularity- isoquercetin& dihydroquercetin i.e. taxifolin (Saehi et al, 2020).

Nanotechnology- Gokhale et al (2019) have successfully used nanotechnology based quercetin hydrogel to attenuate the osteoarthritis \textit{in vitro} and \textit{in vivo} in Maharashtra state, India, setting the stage for its clinical trials with proper regulatory approvals and precautions in India. A nanotech study in Pune city, Maharashtra state, India to showed effectiveness of Chitosan based topical application of Quercetin loaded transfersome to be effective in osteoporosis (Pandit et al, 2020).

We suggest experimenting with Glycine conjugation with Quercetin for grater efficacy and glutathione status improvement, thus improving body’s own healing system, hormonal balance. For, Glycine is anon polar amino acid that makes the glutathione and is found to attenuate osteoarthritis (Paz Lugo et al, 2018). Non polar amino acid conjugation is suggested as a techniqueto improve quercetin bioavailability 3-10 fold (Arifian et al, 2022). This is akin to the Ayurveda principle that body heals itself & medicines only aid in the process & also the postulate of Hippocrates of self-healing (Chu et al, 2022).
REFERENCES


