REVIEW

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Quercetin: health benefits with relevance to TNF-α-linked inflammatory diseases

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Abstract: With increasing interest among the general public for using natural and herbal remedies, there is a great need to document and list ancient medical texts and practices, as well as to investigate the efficacy of a number of 'ancient' compounds that are currently reputed to have medicinal benefits for such diseases as arthritis, wound healing, cancer, chronic inflammation and cardiovascular disease. With these goals in mind, we have collected evidence for the use of the natural polyphenolic flavonoid quercetin in antiquity, as well as identified modern clinical research showing the efficacy of this compound for human health. Our report not only provides clear evidence for the flavonoid quercetin as an anti-inflammatory, which may well have been used in antiquity to treat arthritic swelling and pain, it also serves to re-educate the general public and scientific community to the fact that natural and herbal remedies can be very efficacious forms of medication, deserving respect.

Key words: flavonoids, fruit, health, quercetin, anti-inflammatory, TNF-α

INTRODUCTION

Common folk-lore remedies have become very popular in recent years because prescribed medicines are marketed at increasingly high prices, and individuals as well as medics have become aware of the adverse side-effects of many medicines [1]. A recent report suggests that perhaps as a consequence 17% of Americans take herb and dietary supplements to treat or control ailments, more often than not compounds with which physicians, pharmacists and nurses have had scant training [2]. However, is there any real evidence that such dietary supplements are efficacious? The aim of the current study therefore was to evaluate the health-benefits of the ancient application, quercetin.

Historical background. In terms of nourishment, the dietary experts in antiquity referred to foodstuffs as having 'strong', 'medium' or 'weak' properties. Celsus, who lived during the reign of Marcus Aurelius, in his work *De Medicina*, written between 175-180 AD, wrote about fruits:

> The weakest of food materials are: all vegetable stalks and whatever forms on a stalk, such as the gourd and cucumber and caper, all orchard fruits, olives, snails, and likewise shellfish [3].

Equally well documented is the detailed knowledge of the pharmacological properties of many extracts of identifiable botanical species that were used in antiquity [3, 4].

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Pomegranates, for example, were introduced into Egypt from Western Asia as early as the New Kingdom (ca. 1550-1295 B.C.) spanning the reigns of Ahmose and Amenhotep I, to Tutankhamun and Horemheb [5]. Furthermore, pomegranate-shaped jars found in Egypt, one originating from Abydos, can be seen at the Metropolitan Museum of Art in New York (objects 26.7.1180 & 44.4.52) [5]. Indeed, the Ancient Egyptians highly prized the drink extracted from pomegranates for its astringent effect, that is to say, something that causes contraction of the skin and thereby reduces bleeding, as well as its ability to shrink tissues and reduce the swelling (e.g. an anti-inflammatory) associated with wounds. The town of Canosa, known to the Romans as Canusium, is to be found in Apulia, southern Italy, and is considered to be the principal archaeological centre of Puglia. It is also one of the oldest continually inhabited cities in Italy. In antiquity, the dead were buried in carefully appointed tombs, and provided with the artifacts they used in life, among them models of pomegranates (Fig. 1).

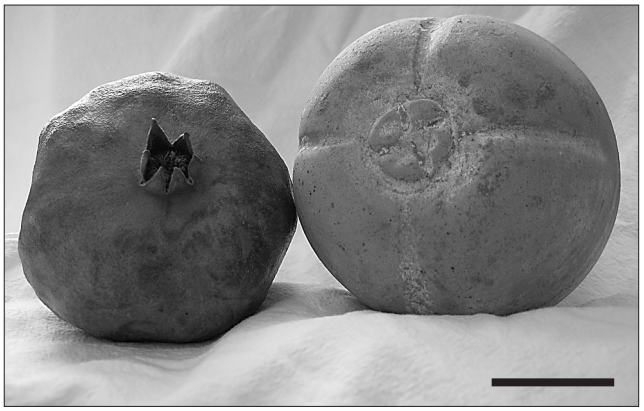

Figure 1 Terracotta model of a pomegranate from Canosa (Roman Canusium) a town in Apulia, southern Italy – 3rd Century BC (right) compared with a ripe fresh pomegranate fruit (left). Photograph by permission from a private collection. The photo was taken using a Canon Digital Ixus 60 camera with 6.0 megapixel resolution, on 11 April 2008; shutter 1/60, f/2.8, focal length 5.8 mm. Scale bar = 5 cm.

Dioscorides (ca. 40-90 A.D.), a learned physician and contemporary of Pliny the Elder, practiced as an army doctor during campaigns in Greece, Italy, Asia Minor and Provence in modern-day France. He subsequently compiling his knowledge of medicinal plants in his volume *De Materia Medica*, in which he wrote about the pomegranate:

> That [pomegranate] which is sharp helps a burning stomach, is more contractive and more diuretic [than those that are sweet], but tastes unpleasant to the mouth and is astringent [4].
> The rinds of pomegranate are also astringent … a decoction of the roots expels and kills worms hidden in the intestines [4].

Fruits and berries are known today to contain natural phytochemical compounds, otherwise known as plant secondary metabolites. This is a diverse group of natural products that are thought to provide plants with some defence against herbivores. One of the main natural phytochemical compounds occurring widely in fruits and vegetables is the polyphenolic flavonoid quercetin. Interestingly, pomegranates represent one of the most concentrated natural sources of quercetin known to man.

MATERIAL AND METHODS

The criteria used in the literature search were both theoretically and practically motivated and adopted from proposed criteria in *The International Classification of Functioning, Disability and Health* – ICF [6]. To be specific, articles were chosen only with an internationally recognised impact factor greater than 0.500, except for *Clin. Vaccine Immunol.*, which currently has no impact factor rating due to its recent launch as an online open access journal. A multitude of sources was used including PubMed, EMBase, Medline, Web of Science, Agricola, and selected internet sites, namely Scirus and Google Scholar. The objective of this article, though, was not to be thoroughly exhaustive, and as a consequence only the most pertinent papers were selected. Other sources, including translated texts and historical books, have been chosen for their relevance and their acknowledged authority in the field.

Scientific articles were also chosen based upon their impact to lifestyle and health with respect to quercetin and flavonoids. The time frame used was principally within the last ten years, although a single non-clinical article from 1985 has been used because of its importance with respect to Tumour Necrosis Factor-alpha (TNF)-α and cellular proliferation. Articles cited can be found on PubMed and Medline and most can be accessed freely.

It is also worth mentioning that the use of medical compounds in antiquity was not only tried and tested over several generations, but there was also a substantial margin of error that was taken into consideration when administering medicines, and treatments that reduced this margin were stigmatised as dangerous.

Finally, the contemporary literature cited is based not only on human clinical studies, but also on both laboratory animal and cell studies where the findings are relevant.

RESULTS

Classification of literature sourced. Literature of relevance to this article, whether historical, clinical or non-clinical in nature, was classified according to type, year of translation or publication, the impact factor of the journal in which it was published, the sample size on which the data and conclusions are based, and finally the number of articles of general relevance that have been excluded in preference for the one selected and cited.

On average, 35% of the articles cited were based on clinical studies, while almost 39% were non-clinical in nature (Table 1). The average impact factor for the two groups was calculated as being 4.010 and 9.996 for the clinical and non-clinical literature sources, respectively. For the clinical sources, six were found to have an impact factor of between 1-5, while two were in the range 6-10. The non-clinical sources tended to be even more polarized, with five having an impact factor of between 1-5, while one was in the range 21-25, and two were a little higher – 26-30 (Table 1).

Table 1 Study type, impact, sample size and exclusion data for articles addressing aspects of quercetin and health interactions or benefits

Category	Study Type	Ref No.	Year	Impact Factor	Sample size	Exclusion
Historical	N/A	3	T 1935	N/A	N/A	N/A
	N/A	4	T 2000	N/A	N/A	N/A
	N/A	5	P 2005	N/A	N/A	N/A
	N/A	39	T 1925	N/A	N/A	N/A
	N/A	7	P 1989	N/A	N/A	N/A
	N/A	8	P 2000	N/A	N/A	N/A
Clinical	O, PR	1	P 2004	9.245	18820	192
	E	2	P 2006	1.091	N/A	236
	R, PR	9	P 1997	3.372	9	163
	C, PR	10	P 1996	5.440	2	396
	C, PR	11	P 1999	2.116	5	29
	C, PR	14	P 2006	2.744	6	24
	CR, R, PR	17	P 1999	3.958	5	6
	C, PR	22	P 1996	4.118	18	3
	CA, PR	27	P 2004	–	1	N/A
	CLR, PR	33	P 2008	2.376	N/A	N/A
	C, O, PR	36	P 2008	1.238	10	4
	O, PR	34	P 1996	4.813	2	2
	C, PR	37	P 2007	3.689	41	N/A
	C, R, DB, PR	35	P 1998	3.689	27	N/A
Non-Clinical	C, PR	12	P 2001	2.270	N/A	6
	PR	15	P 1998	1.109	N/A	75
	R, CR, PR	13	P 2006	2.967	N/A	1
	C, PR	16	P 2005	2.967	N/A	256
	PR	18	P 2006	N/A	N/A	67
	PR	19	P 2003	28.697	N/A	2162
	C, PR	20	P 1999	26.595	N/A	58
	PR	21	P 1985	24.595	N/A	937
	PR	23	P 2005	0.764	N/A	1
	C, PR	29	P 2002	-	150	N/A
	C, PR	40	P 2008	2.376	N/A	N/A
	C, PR	32	P 2007	3.846	N/A	6
	C, PR	24	P 2006	1.504	N/A	27
	PR	42	P 2009	2.049	N/A	N/A
	PR	41	P 2003	4.006	N/A	N/A
Statistics	Clinical 14	Of 35	Mean	3.420	1353	75
	Non-Clin. 15	Of 35	Mean	6.916	10	239

C = controlled study; O = observational study; CR = crossover study; E = editorial; R = randomized; CA = case report; DB = double blind; CLR = clinical review; PR = Peer-reviewed; T = translated; P = Published.

Biological advantages of pomegranate and agricultural importance. The pomegranate (*Punica granatum* L.; *inhmn* in ancient Egyptian) grows wild in south-west Asia and is cultivated in Mediterranean countries. It is a deciduous shrub or tree with scarlet, scented flowers, and later, a hard yellowish to reddish fruit which contains bright-red seeds. The tree was introduced into Egypt in the New Kingdom (1570-1070 BC) *via* Mesopotamia and Phoenicia; furthermore, it is known to have been present in the garden of Ineni at Thebes [7].

Pomegranate has been used by man to treat dysentery, diarrhoea and stomach ache in man, as well as to treat roundworm infections in man and livestock [7, 8]. Indeed, the bark of the root contains several alkaloids which are thought to be instigative in the expulsion of intestinal worm infections, including those by tape-worms. The rind of the fruit, which contains 28% gallo-tannic acid, is thought to be the source of the dysentery, diarrhoea and stomach-ache alleviating effects associated with this plant [8].

Scientific evidence of the effects of quercetin. Foods, in which quercetin is conjugated with glucose, show an enhanced absorption of nutrients from the gut [9]. However, there are differences between dietary sources, with the bioavailability of quercetin from apples being 30% relative to that of onions [9]. Moreover, absorption and elimination occurs slowly throughout the day [10]. Food processing is also not without significance, as an investigation of fried onion consumption resulted in increases in quercetin levels from baseline to peak within a two hour period [11], and the addition of milk was shown to have no affect on the absorption of flavonols present in tea [12].

The quercetin present in onion soup inhibits some aspects of collagen-stimulated platelet aggregation and signalling. Hubbard et al. [13] found that the collagen-stimulated tyrosine phosphorylation of a key component of the collagen-signalling pathway *via* glycoprotein VI is inhibited by ingestion of a highly concentrated quercetin soup.

Recently, an investigation of tomato juice containing quercetin-3-rutinoside (rutin) showed that the large intestine plays a role in the metabolism of this flavonoid, resulting in the catabolites, 3,4-dihydroxyphenylacetic acid, 3-methyl-4-hydroxyphenylacetic acid and 3-hydroxyphenylacetic acid in urine [14]. This work confirms earlier findings of metabolism of flavonoids in the liver and colon, with O-methylation, sulfonation and glucuronidation of hydroxyl groups in the former, and bacterial ring fission of flavonoids in the latter [15]. Furthermore, Fiorani and Accorsi [16] have shown that such metabolites of quercetin can enter erythrocytes and donate electrons to the plasma membrane oxidoreductase. Indeed, it has been known for some years that fruit juice consumption has a pro-oxidant effect on plasma proteins and increased glutathione peroxidase activity, attributable presumably to several components in the juice, among them quercetin [17]. Moreover, quercetin is known to act as a dietary anti-oxidant attenuating the oxidation of low-density lipoproteins *in vitro* by scavenging free oxygen radicals [10].

While the bioavailability of the compound quercetin and the site of absorption in the gastrointestinal tract seems dependent on dietary source, food processing and the type of sugar to which it is bound, recent research now indicates that quercetin inhibits the pro-inflammatory cytokine TNF-α at the gene expression level [18].

The tumour necrosis factor was initially discovered as a result of its anti-tumour activity, but has now been shown to mediate tumour initiation, promotion, and metastasis [19]. Indeed, in mice deficient in TNF-α, there is a high degree of resistance to skin carcinogenesis [20]. In addition, the induction of pro-inflammatory genes by TNF-α has been linked to a great many diseases, with expression of inflammatory genes including cyclooxygenase-2 (COX-2), lipoxygenase-2 (LOX-2), inflammatory cytokines and chemokines. Moreover, TNF-α has been found to be a growth factor for most tumour cells, e.g. ovarian cancer cells, cutaneous T-cell lymphoma, leukaemia, renal cell carcinoma, and Hodgkin's lymphoma (21). Besides which, a study by Malaveille et al. [22] suggests that smokers ingesting dietary phenolics are partially protected against the harmful effects of tobacco carcinogens on bladder mucosal cells.

Because of the critical role of TNF-α in mediating tumorigenesis and inflammation, agents that can suppress TNF-α activity have enormous potential for therapy in TNF-α-linked diseases. To this end, flavonoids have been reported to be beneficial in lowering inflammation and oxidative stress, as well as having a positive effect in cancer and chronic inflammatory diseases through their suppression of TNF-α synthesis and systemic release [23].

In a recent cell culture study involving the application of quercetin to rabbit synoviocytes (HIG-82), it was found that this particular flavonoid inhibited neutrophil activation and synoviocyte proliferation [24]. These authors concluded that quercetin may have therapeutic potential for the treatment of monosodium urate or calcium pyrophosphate 'micro-crystal' induced arthritis or rheumatoid arthritis. Typically, quercetin was shown to have an IC_{50} in terms of HIG-82 rabbit synoviocyte viability at a concentration of 45 μM, and induce *ca*. 30-40% inhibition at concentrations <10 μM [24]. Drugs such as camptothecin have been shown to inhibit some aspects of micro-crystal induced arthritis (CIA), but drugs rarely inhibit both crystal-induced neutrophil activation and survival aspects of CIA [25]. Moreover, while such drugs as methotrexate and paclitaxel may offer effective treatments for arthritis, they also cause significant systemic toxicities [26], and methotrexate has no inhibitory effect on neutrophil activation [24].

Regulators of TNF-α release in the body are currently a focus of interest as this particular compound has been linked to the incidence of such diseases as Crohns, Alzheimers, Rheumatoid Arthritis, Psoriasis and Ankylosing Spondylitis. Indeed, antibodies raised against TNF-α are now commercially available under prescription and are proving beneficial for many patients, albeit with a high cost of treatment (ca. € 9,300 or US $ 14,700 per patient per year) to the health system and society. Perhaps future advances in the regulation of TNF-α are to be found in the past, incurring a much lower financial burden to society through the example of the Ancient Egyptians and Romans and their use of pomegranate juice.

Side effects of quercetin. In an isolated clinical case report published by Reid et al. [27], a 69-year-old male diagnosed with carcinoma of the lung as a consequence of metastasis, began self-treatment with quercetin (400 mg/day) and bromelain (100 mg/day). After ca. 5 weeks, he was found to have elevated liver enzymes, e.g. AST (265%), Alk Phos (140%) and LD (112%) *cf.* basal values. Upon cessation of quercetin and bromelain self-treatment, the patient was found to have normal enzyme levels *ca*. 14 days later [27]. In a Naranjo adverse drug reaction probability evaluation, this event scored

a 6, indicating a probable association between the adverse drug reaction and the quercetin/bromelain medication [28]. However, as always, a considerable degree of caution should be used when assessing the direct applicability of single case reports.

On a more positive note, however, a study of mice receiving chronic morphine (10 mg/kg sc) reported a loss of their tolerance to the antinociceptive response when treated simultaneously with 25 or 50 mg/kg po quercetin, respectively [29]. Quercetin, which is known to inhibit the formation of inflammatory mediators prostaglandins, may well suppress the documented morphine-induced rise in prostaglandins [30], which is reported to have a role in the development of tolerance to morphine with time [31]. Further studies are needed, but it seems that quercetin may be useful in the treatment of morphine withdrawal syndromes, e.g. abdominal cramps and diarrhoea.

In a cell culture study involving the application of quercetin to a rat lung epithelial cell line (RLE), it was found that hydrogen peroxide damage to DNA could be prevented through pre-treatment with quercetin (30 min. for 100 μM quercetin). However, it was also found that quercetin, in the presence of hydrogen peroxide, resulted in a significant ($P<0.05$) lactate dehydrogenase (LDH) leak from RLE cells [32]. While this study clearly shows that quercetin has a beneficial effect as an efficient scavenger of such free radicals as hydrogen peroxide, it reportedly also sets in motion toxic changes that result in a loss of LDH from RLE cells, which will ultimately affect cell viability [32]. Thus, it would seem that the apparent protection offered by quercetin is in reality an exchange of one form of toxicity (e.g. free radical DNA damage) for another.

Pharmacokinetics and clinical effects of quercetin. In terms of quercetin absorption, the most likely candidate appears to be the sodium-dependent glucose transporter-1 of the small intestine [33], with values for plasma levels of quercetin generally in the low nanomolar range, although dietary supplementation can result in a plasma increase up to the high nanomolar to low micromolar level [34, 35]. Moreover, the average peak plasma concentration of quercetin for ten subjects following a 500 mg oral dose in a recent clinical study, was measured as being 463 ng/ml some 3.5 hours after ingestion with an average terminal half-life in plasma of 3.5 hours [36].

Only two studies have been reported regarding the effects *in vivo* of quercetin in patients suffering from a disease which involved oxidative stress or inflammation. In one of the studies, four weeks of 730 mg of quercetin ingested daily caused a significant reduction in systolic, diastolic and mean arterial pressure in stage 1 hypertensive patients. Remarkably though, no alteration in blood pressure was found in a group of pre-hypertensive patients, suggesting that the beneficial effect of quercetin can only be expected when basal levels of damage are increased [37].

In the second study, the effects of quercetin on patients suffering from sarcoidosis were assessed, with particular emphasis on the characteristic increased levels of pro-inflammatory cytokines TNF-α and IL-8 which typify this disease [38]. After 4 × 500 mg quercetin in a 24 hour period, the antioxidative defence system of these patients was found to be improved, and markers of both oxidative stress and inflammation had been reduced [33].

DISCUSSION

Clearly, the advantage of the anti-inflammatory role of quercetin in pomegranates has been known by mankind for about 3,500 years. In antiquity, it was necessary to consider the preservation of fruits, and with this in mind, Pliny the Elder (ca. 23-79 A.D.) advised in his work entitled *Natural History*, that:

> Pomegranates should be hardened by hot sea water, then dried in the sun for three days and hung up in such a way as to be protected from the dew at night. When wanted they should be thoroughly washed in fresh water [39].

Today, one can buy refined quercetin in capsule form at very little expense, and enormous benefit to those suffering from for example arthritis in their hands, knees, feet and hips. It is harmless if taken at a level of up to 750 mg/day, unless one is allergic to fruit and vegetables; it acts rapidly within a few days to ease the swelling of inflamed joints, and in so doing it banishes pain. Furthermore, there is some evidence that quercetin, which is a strong anti-oxidant, provides protection against cardiovascular disease when consumed on a regular basis.

Furthermore, the dietary uptake of flavonoid-rich plants is believed to be associated with a lower incidence of osteoporosis [40]. Quercetin has been the specific focus of attention in this field due to its ability to inhibit bone resorption in rabbit mature osteoclasts, promote osteoclast apoptosis, and prevent bone loss in ovariectomized rats [41].

Finally, in a recent study of the monoamine oxidase A inhibitory activity of extracts of *Calluna vulgaris,* which has long been used as a Danish traditional medicine against both the common cold and rheumatoid arthritis [42], revealed a IC_{50} for monoamine oxidase A by the quercetin extracted from this plant of 18 μM. These authors concluded that the quercetin content of *Calluna vulgaris,* an effective inhibitor of monoamine oxidase A involved in the metabolism of exogenous amines and the regulation of neurotransmitters, was most likely to be an effective nerve calmative [42].

Clearly, the potential of quercetin in modern day medicine appears far reaching, although it remains essential, more so now than at any other time in history, that the general public should be re-educated to the fact that natural and herbal remedies are very effective forms of medication. Therefore, they should be treated with a great deal of respect.

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