Review

Red wine antioxidant properties implications in rheumatic diseases: exploring clonal variations in resveratrol and other bioactive compounds

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ABSTRACT

Resveratol (RS), a non-flavonoid poly-phenol, is a well-recognised anti-in-flammatory compound of red wine. This narrative review aims to explore the mechanisms underlying its potential antioxidant properties in osteoarthritis (OA), rheumatoid arthritis (RA), spondyloarthritis (SpA), and osteoporosis (OP), as well as its clonal variation in red wine and future perspectives for clinical applications.

Although human data remain limited and sometimes controversial, recent studies in animal models have demonstrated that RS can reduce inflammation by interacting with various cellular pathways, including the activation of sirtuins, which regulate oxidative stress and bone density in OA and OP, and modulating gut microbiota, as central inflammatory trigger for SpA and RA.

While RS effects and toxicity are dose-dependent, its concentration in red wine may vary depending on grape clone selection and maceration time, potentially increasing its levels and associated health benefits. Additionally, pterostilbene, a compound structurally related to RS, has shown greater bioavailability and promising antioxidant effects. The rapid metabolism of RS in the human body remains a limitation for its therapeutic use, which might be improved through combination with other antioxidants such as vitamins C and E, curcumin, and quercetin, offering synergistic anti-inflammatory effects.

Moreover, advanced delivery systems, including nanotechnology, have been developed to enhance RS absorption and stability. Continued research is essential to better understand the role of RS and other antioxidants, and to optimise their therapeutic potential in the near future.

Introduction

Wine is one of the most widely consumed alcoholic beverages globally, produced through the fermentation of grape must. Its regular consumption dates back to ancient civilisations, including the Egyptians, and today, production levels reach approximately 250 million hectoliters annually. Alcohol assumption, especially when excessive, is often regarded as a factor that disrupts metabolic balance. However, its impact is dose-dependent and can differ depending on the method of intake. Notably, moderate consumption of red wine appears to have a beneficial effect on pro-inflammatory cytokines (1). However, numerous studies have demonstrated that a reasonable drinking can offer health benefits, largely due to the antioxidant properties of its polyphenolic compounds (2-4). These beneficial effects may help combat neurodegenerative and age-related diseases, cancer, diabetes, obesity, and cardiovascular conditions, potentially increasing life expectancy compared to both heavy drinkers and abstainers. Red wine is primarily composed of water (85%) along with ethanol (13%), glycerol, higher alcohols, polysaccharides, organic acids, polyphenols (around 0.1%), and other trace compounds. Among these, polyphenols are the most significant group, largely contributing to the colour and flavour of wine. Polyphenols can be classified into flavonoids and non-flavonoids (5-7). Flavonols play a critical role in sensory perception and contribute to the colouration of wine, often in combination with anthocyanidins. Non-flavonoid compounds encompass stilbenes and phenolic acids. Among stilbenoids – hydrocarbons primarily found in the skins and seeds of grapes (8-10) – res-
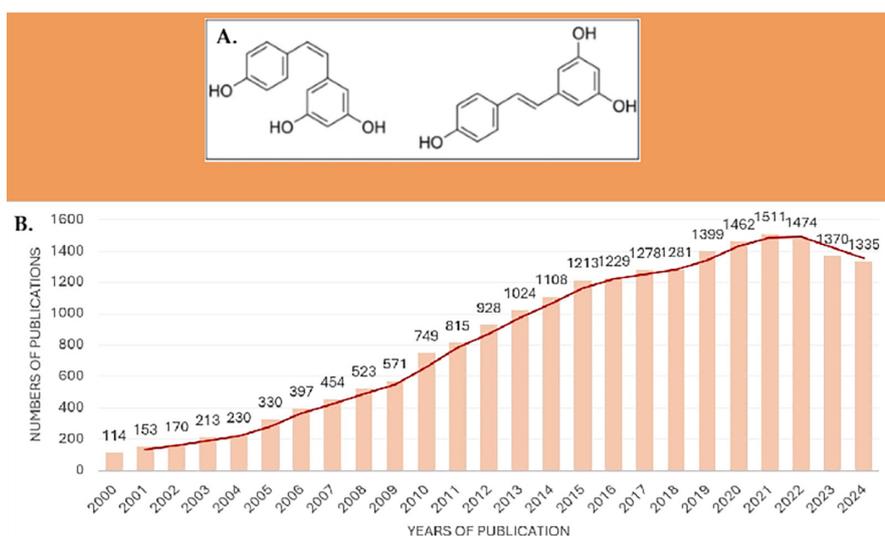
Fig. 1 A: Chemical structures of cis- [(Z)-RS on the left and trans-RS [(E)-RS, on the right.
B: 21,331 publications per year related to the term 'resveratrol' on PubMed since 2000, with a two-year moving average trendline displayed in red.

veratrol (RS) is the most widely known. Discovered around 1940 and studied in over 70 plant species (11), RS exists in both cis- and trans- forms (trans-3,5,4'-trihydroxystilbene), as well as in glucosylated variants such as piceid (RS-3-O-beta-D-glucoside) (12-15) (Fig. 1A).

Even if numerous studies have demonstrated a potential role of RS (Fig. 1B) and of pterostilbene (PTE) – a stilbenoid related to RS – to prevent a wide range of diseases, their antioxidant properties remain still misunderstood among clinical practitioners, due to lack of clinical trials and its rare employment in routinary practice, especially in European countries.

However, the discover of cardio-prophylactic effects of red wine in high saturated fat diet, commonly known as 'French paradox', was the modern watershed for the interest of modern medicine on RS properties (16), as part of the great research area on environmental factors in inflammatory diseases (17). The influence of diet (18) and microbiota (19) on the natural history of many rheumatic diseases is well recognised, even if with significant limitations for standardisation due to multifactorial pathogenesis and comorbidities. Red wine and RS have gained an increasing attention in the last years, representing a fascinating young field of study. In fact, progress has been hindered by the complexity of integrating insights from multidisciplinary fields and the difficulty to study human models, for the potential side effect of alcohol intake. Initial studies on osteoarthritis (OA) (20, 21), fibromyalgia (22), adjuvant (23), and rheumatoid arthritis (RA) (24) and gout (25) investigated the role of RS in symptom relief, even if its use as supplementary treatment to reduce pain and inflammation is not commonly diffused in daily clinical practice until now. Furthermore, a pleiotropic effect of RS, on systemic inflammation and cardiovascular disease of spondyloarthritis (SpA), was also postulated, due to reduction of immune cells activation and improvement of autophagy (1). Finally, contrarily to most known theory of alcohol intake as risk factor for osteoporosis (OP), some new evidences on red wine showed that, when moderately assumed, might paradoxically give potential benefit against risk facture (26-28). The aim of this narrative review is to explore the benefits of RS contained in red wine on OA, RA, SpA, and OP and the potential mechanisms at the basis of its antioxidant properties; we also investigated the possible clonal variation of RS in different cultivar and the possible future clinical use perspectives in rheumatic diseases.

Materials and methods
The articles selected for this narrative literature review were searched on Google Scholar, Web of Science, Scopus and PubMed until 25th November 2024 and regardless of the date of publication, using the following PubMed Mesh terms: (resveratrol AND osteoarthritis, AND rheumatoid arthritis, AND spondyloarthritis, AND osteoporosis) (Fig. 1B). Additionally, the references of relevant articles were hand-searched for the identification of other potentially suitable papers on humans and cellular or animal models. Based on the paucity of studies on humans and for the great variety of method lies used, we chose a non-systematic structure for this review. For this reason, we will not provide the flow chart of literature selection. Subsequently, the search strategy was not registered in PROSPERO or other specific databases for systematic reviews and was exclusively focused on identifying original full-text articles. Zotero was only used for references final revision. Conference abstracts, commentaries, and editorials were excluded. However, letters and relevant review articles providing sufficiently detailed data and methodology were considered for inclusion in the review. Successively, papers were assessed for level of evidence using an adapted version of modified-Newcastle Ottawa Scale (m-NOS) for case-control and cohort studies based on three domains: selection (maximum of 4 for cohort studies, 5 for case-control studies), comparability (maximum of 2), exposure (maximum of 3 for both) (Table III).

Results
Resveratrol benefits
The most important (middle-high quality m-NOS assessed) studies about the effects of RS on cellular inflammatory pathways of rheumatic diseases were reported in Table I, derived from more preclinical studies on animal and cellular models than research on human subjects. Initial studies in rats with induced osteoarthritis (OA) showed that resveratrol treatment reduced mechanical hypersensitivity, heat-induced hyperalgesia, and the expression of pro-inflammatory markers such as COX-2 and iNOS mRNA. These effects were measured at days 0, 7, and 14, and were comparable to those observed with the reference

Table I. Most important studies on osteoarthritis, osteoporosis, rheumatoid arthritis and spondyloarthritis were categorised as of poor (0-3), fair (4-6), or good/high (7-9) quality based on their total modified Newcastle Ottawa (m-NOS) score.

Rheumatic diseases	First author, year of publication	Type of study, human or models, numbers of patients if applicable	Parameters studied and duration of follow-up	Main results	m-NOS levels (0-9)
Osteoarthritis	Nguyen, 2024	Randomised placebo controlled, humans, 71 OA treated *vs.* 71 OA with placebo	Knee pain, WOMAC function, and patient global assessment, 3 months	Not significant	7 (good-high)
	Wang 2016	Randomised placebo controlled, rats, 10 OA treated with RS (5mg/kg and 10mg/kg) *vs.* 5 OA with placebo, 5 OA with eterocoxib and 5 healthy	Heat and cold hyperalgesia, movement measurement, serum and synovial cytokines and osteocalcin, histological analysis, 0-14 days	Increase of movement and osteocalcin, decrease of cytokines, in OA treated with RS and eterocoxib	7 (good-high)
	Wendling 2016	Case controls, Humans, 19 OA *vs.* 18 healthy *ex vivo* peripheral blood cells treated with RS	Nuclear and cytoplasmic Sirt1 activity and cytokines (TNF-α, IL-6, IL-8) by the cells cultured for 48 h	Similar increase of Sirt1 protein expression and activity; significant dose-dependent increase in IL-6 levels only in OA	5 (fair)
Osteoporosis	Yang 2019	Randomised placebo controlled, rat models and osteoblast culture of 10 OP treated, 5 OP, 5 healthy	DEXA and SIRT1, 8 weeks	BMD increased in low and high RS (but dose-dependently) treated groups compared to OP. RS increased SIRT1	8 (good-high)
	Wang, 2016	Randomised placebo controlled, rat models and osteoblast culture of 10 OP +low- RS (5mg/kg), 10 OP+ middle-RS (25mg/kg) 10 OP+high-RS (45mg/kg), 10 OP, 6 healthy	BMD, bone samples for femur strength, SIRT1 and NF-kB pathways, 8 weeks	BMD, femur strength and SIRT1 increased, and NF-kb decreased, only in middle and high RS treated rats (not in low dose)	8 (good-high)
Rheumatoid arthritis and spondylo-arthritis	Lomholt, 2018	Case control, humans, 7 RA, 7 SpA, treated with RS alone *vs.* in combination with MTX or adalimumab	MCP1 and MMP3 levels in synovial fluid culture, either 48 h or 21 days	Only MCP1 decreased significantly, greatly in patients with low diseas activity (DAS28CRP ≤3.2), in high lymphocyte fluid count and in combination with MTX	5 (fair)

DEXA: dual-energy x-ray absorptiometry; MCP1: monocyte chemoattractant protein 1; MMP3: matrix metalloproteinase 3; MTX: methotrexate; SIRT1: sirtuin 1.

drug etoricoxib. These findings suggest that resveratrol may exert a protective effect in OA by inhibiting the iNOS/COX-2 signalling pathway (29).

Unfortunately, only one study (20) was registered as a randomised controlled trial evaluating RS monotherapy in human subjects compared to placebo, and it did not yield significant results. However, the study relied solely on subjective measures such as pain scores and global clinical assessment, was limited in duration (three months), included a small sample size, and did not assess specific biochemical markers of OA. Furthermore, the potential interaction with other drugs in rheumatic patients has not been further investigated, except in the study by Lomholt *et al.*, which examined the anti-inflammatory effects of RS alone or in combination with methotrexate (MTX) or adalimumab. This study focused on synovial fluid mononuclear cells from a limited number of patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA), demonstrating that RS may significantly reduce the production of monocyte chemoattractant protein-1 (MCP-1 or CCL2) – a key cytokine involved in chemotaxis during innate immune responses – particularly when combined with MTX and in patients with low disease activity (30).

Furthermore, we did not find other evidence of possible RS association with biological or synthetic disease-modifying drugs, steroidal or non-steroidal anti-inflammatory treatments, such as possible interactions and consequences on RS toxicity or pharmacokinetic mechanisms.

SIRT1 pathways of resveratrol
Sirtuin 1 (SIRT1) is a longevity-associated protein initially identified as a regulator of lifespan. In recent years, it has been shown to modulate key signalling pathways and participate in various biological processes related to bone aging and osteoclastogenesis (31), as well as cartilage homeostasis (32). SIRT1 regulates the expression of extracellular matrix proteins and helps prevent chondrocyte apoptosis (32).

Initial studies investigating the cognitive benefits of RS have suggested that it may also play a key role in regulating apoptosis and autophagy, potentially through the activation of SIRT1. These findings point to a promising therapeutic strategy targeting aging-related mechanisms (33, 34).

A study conducted on animal models and osteoblast culture examined the effects of different doses of RS on bone metabolism. The results showed a cor-

relation between RS levels and reduced bone resorption rates, with therapeutic efficacy observed even at low doses (35). Notably, bone mineral density (BMD), as measured by DEXA, was higher in RS-treated osteoporotic (OP) groups after 8 weeks of treatment compared to the OP control group, with a more pronounced increase in the high-dose RS group. Furthermore, RS treatment in osteoblast cultures from the same experimental model protected the cells by activating the SIRT1 signalling pathway and enhancing mitophagy through upregulation of SIRT1 expression.

Otherwise, in another previous model of OP-induced rats, RS demonstrated to increase SIRT1 expression, significantly improving BMD, SIRT1 levels and femur strength, only in middle and high dose treatment (36).

Unfortunately, these evidences are mostly limited only to animals and *in vivo* and *in vitro* animal models.

In fact, only one study, on a limited number of human subjects and for a very limited time of observation, showed, in *ex vivo* peripheral blood mononuclear cells, that SIRT1 upregulated activity after RS treatment was similar in OA and healthy controls and that RS at high dose might only increase IL6 levels (37).

Gut microbiota
In rheumatic diseases, microbial dysbiosis of gut commensals has been linked overall to RA and SpA and appears to play a key role in the associated gut inflammation. In particular, the 'gut-synovial axis' was hypothesised as a link between SpA and inflammatory bowel diseases (IBD) (38-42).

Most of SpA patients showed gut microbiota disorders (43), with a distinct microbial profile that has been associated with fecal calprotectin levels (44). In particular, an increased abundance of *Enterococcus faecalis* was particularly noted appearing to play a different role compared to *Lactobacillus plantarum*, *rhamnosus* and *acidophilus,* in patients with IBD in remission or with mild symptoms (45).

Given its generic influence on intestinal homeostasis, the impact of RS on gut microbiota has been investigated, show-ing potential benefits on bowel permeability and secondarily in modulating inflammatory responses (46, 47).

Unfortunately, RS use seemed to be limited by low absorption rates in the gastrointestinal tract, rapid metabolism, and rapid excretion (48).

In fact, although only 14% of the initially administered RS dose was detected in the intestine at its peak (4 hours post-administration) and was primarily found in the small intestine and feces, RS sulfate metabolites – rather than RS itself – significantly promoted the growth of Lactobacillus reuteri (by tenfold) and markedly upregulated the mRNA expression of tight junction and mucin-related proteins (48). For this reason, its use has been proposed in IBD, which is frequently associated with SpA (49).

In murine models of SpA, researchers found that intragastric administration of resveratrol (20 to 50 mg/day for 4 weeks) reduced disease severity by suppressing the TLR4/NF-κB/NLRP3 signalling pathway, restoring intestinal mucosal barrier function, and modulating gut microbiota composition. Specifically, it increased the abundance of Lactobacillus and Bifidobacterium, while reducing levels of Enterococcus faecalis and Escherichia coli (46).

Additionally, the interaction between RS and gut microbiota has been hypothesised to support metabolic balance and help prevent obesity, both of which are recognised risk and severity factors for rheumatic diseases (50). This effect may contribute to reductions in body weight and fat levels. However, human studies on metabolic syndrome have produced inconsistent and conflicting results (47), possibly due to the ability of RS to alter bacterial populations (48).

Finally, *Porphyromonas gingivalis*, a Gram-negative anaerobic bacterium, has gained attention for its involvement as an inflammatory trigger and progression factor in RA (51). Although there is limited evidence that RS may exert a protective role on oral microbiota (51-52) and specifically on Porphyromonas gingivalis (53), the impact of RS on oral microbiota is RA has not been yet studied. Future research may explore its potential effects on this important pathogenetic factor.

Clonal and family variation of resveratrol
Due to its widespread popularity, red wine is produced across the globe under varying temperatures, altitudes, and production methods, resulting in a wide variety of types. Some well-known examples include Merlot, Cabernet Sauvignon, Pinot Noir, and Chianti Classico. Key differences between red wine varieties lie in their flavour profiles, production techniques, regions of origin, and chemical composition. Alongside the broad range of red wine types, there are also vine clones, genetically selected variations developed to enhance specific characteristics as needed. Studies highlight red wine clones with RS concentrations that differ from the standard varieties (54) (Table II).

These findings suggest that modifying the genetics of standard grape populations can increase the overall RS content in the resulting wine, also based on specific variations between clones (14) and in respect of duration of maceration process length (1, 5, or 10 days) (15) (Table III). In fact, a more prolonged maceration times lead to higher RS content (15).

Pterostilbene (PTE), or trans-3,5-dimethoxy-4-hydroxystilbene, is a stilbenoid compound found in grape skins, blueberries, and peanuts (55), and belongs to the same chemical family as resveratrol (RS). Similar to RS, PTE has been associated with several health benefits, including lifespan extension, antioxidant and anti-inflammatory effects, and protection against cancer, diabetes, cardiovascular, and neurodegenerative diseases (56). The main structural difference between RS and PTE lies in the presence of two methoxyl groups in PTE, which enhance its bioavailability and systemic concentration (57). However, despite its superior absorption, only a limited number of *in vitro* and *in vivo* studies suggest that oral administration of PTE may have a protective role in acute and chronic inflammatory conditions (58).

In animal pivotal models, PTE can reduce oedema, inflammatory cells infiltration and fibrosis (58-59). Furthermore, *in vitro* researches showed that

Table II. Adapted from the Besrukow *et al*. data (54), this table shows the total content of RS across a wide range of red wine cultivars, including their rootstocks and, where applicable, clone types.

V. vinifera L. cultivar	Clone	Rootstock	Resveratrol	Total
Rondo (PIWI) [RL8]	10 Gm	Boerner	3570 ± 100	7748 ± 586
Barbera Nero	84	Kober 125AA	2466 ± 184	6435 ± 315
Pinot Noir	20-13 Gm	Boerner	3895 ± 337	5786 ± 571
Bastardo	NA	Boerner	2474 ± 94	5700 ± 777
Cabernet Sauvignon	R5	Boerner	2758 ± 69	5613 ± 535
Zweigelt	NA	Boerner	2459 ± 370	5568 ± 470
Gamay Noir	509 INRA	Boerner	3215 ± 321	5458 ± 498
Touriga Nacional	NA	Boerner	1959 ± 114	5145 ± 156
Trincadeira	NA	Boerner	2177 ± 61	5043 ± 179
Teinturier	NA	Kober 5BB	2563 ± 53	4955 ± 103
Pinot Meunier	NA	Boerner	2496 ± 89	4940 ± 227
Rubintos	NA	Boerner	2957 ± 2	4808 ± 55
Ancelotta	F 18	Kober 5BB	2159 ± 19	4761 ± 141
Merlot Noir	INRA 346	SO4	2640 ± 140	4652 ± 380
Syrah	99	Boerner	2244 ± 32	4640 ± 177
Nero (PIWI) [RL5]	NA	Boerner	2895 ± 90	4493 ± 318
Pinot Tete de Negre	NA	Kober 125AA	2638 ± 47	4458 ± 291
Ramisco	NA	Boerner	2192 ± 94	4358 ± 672
Deckrot	NA	Boerner	2201 ± 98	4042 ± 220
Nebbiolo	R 6	Boerner	1987 ± 34	4037 ± 91
Cabernet Franc	214 INRA	Boerner	2351 ± 225	3996 ± 262
Shanii Chernyi	NA	5C Gm	2617 ± 268	3929 ± 379
Medoc Noir	NA	Boerner	145 ± 8	3884± 359
Heroldrebe	NA	Boerner	1153 ± 94	3864± 168
Sangiovese Brunello	NA	Boerner	1783 ± 18	3738± 65
Medina	NA	Boerner	2400 ± 192	3718± 239
Tinta Barocca	NA	Boerner	1306 ± 84	3373± 188
Maroo Seedless	NA	Kober 125AA	2322 ± 41	3332± 99
Schiava Grossa	We 4-7	Boerner	1112 ± 7	3329± 89
Sousao	NA	Boerner	1342 ± 7	3215 ± 156
Touriga Franca	NA	Boerner	992 ± 92	3136 ± 348
Färbertraube	NA	Boerner	1142 ± 33	3136 ± 102
Blauer Gelbhölzer	NA	Kober 125AA	1520 ± 32	3011 ± 63
Grenache	NA	SO4	1590 ± 66	2911 ± 141
Sangiovese	R10	Boerner	917 ± 65	2789 ± 115
Zinfandel	NA	Kober 125AA	479 ± 117	2752 ± 189
Pinotage	NA	Kober 5BB	1806 ± 31	2645 ± 335
Rotberger	32-38 Gm	Boerner	859 ± 1	2632 ± 295
Samtrot	We 805	Boerner	668 ± 152	2481 ± 289
Kolor	NA	Boerner	815 ± 55	2255 ± 138
Dornfelder	NA	Boerner	637 ± 146	2201 ± 266
Dakapo	1 Gm	Boerner	930 ± 36	2194 ± 106
Moreto	NA	Boerner	993 ± 32	2106 ± 70
Blauer Frühburgunder	4 Gm	Boerner	238 ± 2	2027 ± 120
Accent (PIWI) [RL7]	1 Gm	SO4	697 ± 149	1905 ± 255
Domina	NA	Boerner	169 ± 0	1851 ± 90
St. Laurent	3 Gm	Boerner	167 ± 5	1838 ± 38
Dunkelfelder	1 Gm	Boerner	91 ± 2	1769 ± 167
Castelao	NA	Boerner	896 ± 17	1730 ± 30
Blauer Limberger	We Elite	Boerner	1023 ± 17	1615 ± 26
Magyar Frankos	NA	Boerner	586 ± 15	1301 ± 23
Tauberschwavz	NA	Boerner	530 ± 6	1215 ± 113
Tempranillo	NA	Boerner	110 ± 2	1037 ± 139
Blauer Portugieser	NA	Boerner	104 ± 3	753 ± 106
Regent (PIWI) [RL7]	NA	Boerner	90 ± 10	631 ± 46

Data are expressed as dry weight (mg/kg ± standard deviation). Resistance level against *Plasmopara viticola* was rated on a scale from 1 to 9. Abbreviation: NA, not applicable; PIWI, Pilzwiderstands-fähige (fungus-resistant) grape varieties; RL, resistance level against *Plasmopara viticola*.

PTE reduces cytokines levels, such as tumour necrosis factor-alpha (TNF-α) interleukin-1β (IL-1β), and interleukin-6 (IL-6), block key signalling NF-κB pathway (60-61) and suppress inflammatory mediators like MMP-2 and MMP-9 (62), offering antioxidant properties against OA and arthritis (63).

Future perspectives and limitations
The pivotal studies on animal and *in vitro* models shown previously, suggested that RS may be carefully considered a promising future therapy in inflammatory and degenerative diseases. Otherwise, the limited number of papers and the heterogenous methodology used in literature might be considered great limits for its immediate diffusion. Firstly, for its limited bioavailability and potential toxicity, the results of RS on humans seemed more restricted than in basic research. For this reason, the association with other antioxidant compounds was postulated to enhance its anti-inflammatory performance and body persistence (Supplementary Table S1).

Ascorbic acid or ascorbate, Vitamin C, present in plants and animals, might reduce and neutralise reactive oxygen species to prevent DNA damage, as well as supporting growth and development in the human body (64). Secondarily, Vitamin E offers also various benefits, such as enhancing protection against bacteria, viruses, and parasites, supporting the immune system, and playing a key role in enzymes involved in signal transduction (65-66).

A recent double-blind clinical trial conducted on 80 postmenopausal women (66) demonstrated that a combination of resveratrol (RS) and vitamin C can reduce oxidative stress parameters. In particular, the group receiving both RS and vitamin C (Group A) showed a significant 33% reduction in lipohydroperoxides, whereas no significant differences were observed in the groups receiving RS alone (Group B) or vitamin C alone (Group C). However, malondialdehyde levels significantly decreased in all three treatment groups – by 26% in Group A, 32% in Group B, and 38% in Group C – compared to the placebo group (67).

Otherwise, like RS, also Vitamin C has its drawbacks. In fact, when vitamin C interacts with transition metals like copper and iron, might have a paradox pro-oxidant activity (68) that can exacerbate infections and cause tooth loss, insomnia, and fatigue.

Limited evidence suggests that resveratrol (RS), when combined with vitamin E *in vitro*, can inhibit the production of inflammatory cytokines

Table III.
A. Average RS concentrations in the standard population and three clones of Vranac vines (14).
B. Average RS concentrations in four clones of Prokupac vines (15).

A	Standard Population	Vranac Clone I	Vranac Clone II	Vranac Clone III
Trans-resveratrol	0.6 ± 0.129	0.485 ± 0.084	0.414 ± 0.062	0.457 ± 0.107
Total resveratrol	2.32 ± 0.317	3.119 ± 0.596	2.416 ± 0.180	2.914 ± 0.317

B	Prokupac clone PR1	Prokupac clone 41/1	Prokupac clone PR6	Prokupac clone PR7
1 day maceration	0.35 ± 0.02	0.41 ± 0.01	048 ± 0.03	0.27 ± 0.01
5 days maceration	0.50 ± 0.02	0.60 ± 0.02	0.63 ± 0.03	0.49 ± 0.02
10 days maceration	0.94 ± 0.04	1.17 ± 0.05	1.46 ± 0.02	0.82 ± 0.04

Data are reported as the mean ± standard deviation, with respect to the duration of the maceration process, with all measurements expressed in mg·L^{-1}

such as IL-6, TNF-α, and IL-1β, while also stimulating macrophage activity. This combination appears to exert a synergistic antioxidant effect (69-70), particularly in OA chondrocytes from animal models, where it significantly reduced the hydrogen peroxide (H_2O_2)-induced inflammatory response (71). Unfortunately, to date, the potential benefits of RS and vitamin E co-administration have not been investigated in Furthermore, the bioavailability of RS has been shown to improve when combined with curcumin in cases of OA and OP (72-73), and with quercetin in OP (73). Both curcumin and quercetin are known for their antioxidant and anti-inflammatory properties (74-75). Firstly, curcumin ($C_{21}H_{20}O_6$), a natural polyphenol extracted from Curcuma longa L., a plant belonging to the ginger family, traditionally, used as a colouring agent, flavour enhancer, and spice, also holds potential applications in the pharmaceutical industry as a powerful scavenger of reactive oxygen species (ROS) (74-76). Furthermore, a possible use of curcumin and RS in early stage of dementia was postulated for a possible controversial role on neuroinflammation (77), with limited efficacy for curcumin (78) and more encouraging benefits on memory performance for RS (79). Secondarily, quercetin ($C_{15}H_{10}O_7$), a flavonoid widely present in various fruits and vegetables (80-81) might alleviate intestinal inflammation via modulating gut microbiota composition (82) and signal transduction pathways and ROS modulation (73) and in animal models, bone health with

a possible underlying regulatory role on NF-B and intrinsic and extrinsic apoptotic pathways in OP (83).
Analogously, even though it is currently still included among recognised OP risk factors, also a moderate alcohol intake seemed to have a controversial protective role on fracture risk, particularly in postmenopausal women (84).
Surely, this association might present future opportunities for rheumatology therapeutic applications. However, further research in clinical trial on humans are required to establish optimal dosage, toxicity levels, and bioavailability to ensure their efficacy and safety in human health
In fact, even if recent studies suggest that its bioavailability and antioxidant properties might be ameliorated by forming complexes with metal ions and other compounds, quercetin's poor solubility, low bioavailability, limited permeability, and instability might still limit its medical applications (80).
Finally, after oral administration, the concentration of RS (free, liquid, or encapsulated) in the body might rapidly decrease (85), with last levels potentially too low to produce significative and persistent impacts on humans. On the other side, higher dosage might be limited by its potential toxicity. Thus, a definitive appropriate dosage remains still unclear, with few and controversial data available in literature, moreover derived by *in vitro* and animal models (86).
Even if RS is generally considered safe and well tolerated in low and moderate doses, it might be also conditioned potentially by unknown other drugs inter-

action. Furthermore, the very high dosage (overall >5 g/day) might release a higher quantity of RS metabolites that have potential adverse cytotoxic effects with gastroenteric (such as diarrhoea and vomiting) and renal complications (86).
Notably, modern research is focused on developing new RS delivery systems. Particularly, in early-stage studies, one widely discussed approach is nanodelivery, a system built using nanotechnology to enhance drug efficiency. It has been shown that RS can overcome its bioavailability barriers when incorporated into nanoformulations, thus improving both its stability and absorption (87-91). Secondarily, Navarro *et al.* (92) have developed a method in which exposing wine grapes to ultraviolet (UV) light increases the production of stilbenes, and consequently RS. Finally, as said in previous chapter, the promising combination of RS with other compounds that play a role of bio-enhancer of RS efficacy and bioavailability (88), might reduce RS potential toxicity (69-70).

Conclusion and take homes messages
Red wine, when consumed in moderation, is recognised not only for its cultural significance but also for its potential health benefits due to the presence of polyphenolic compounds such as RS in terms of protection against neurodegenerative and cardiovascular diseases.
RS has shown also potential anti-inflammatory effects on rheumatic diseases, including RA, SpA, OA, OP, by exerting antioxidant action supported previously by *in vitro* and *in vivo* studies on animal models and with controversial results on very few issues on humans.
Actual limits for clinical trials are still represented by the potential loss of efficacy of RS for its rapid metabolic washout, the uncertain interaction with other drugs and its possible dose dependent effect and consequent toxicity.
Since therapeutic levels of RS cannot be achieved solely through a normal diet, its use should be considered only under medical supervision and as a complement to conventional treatments.
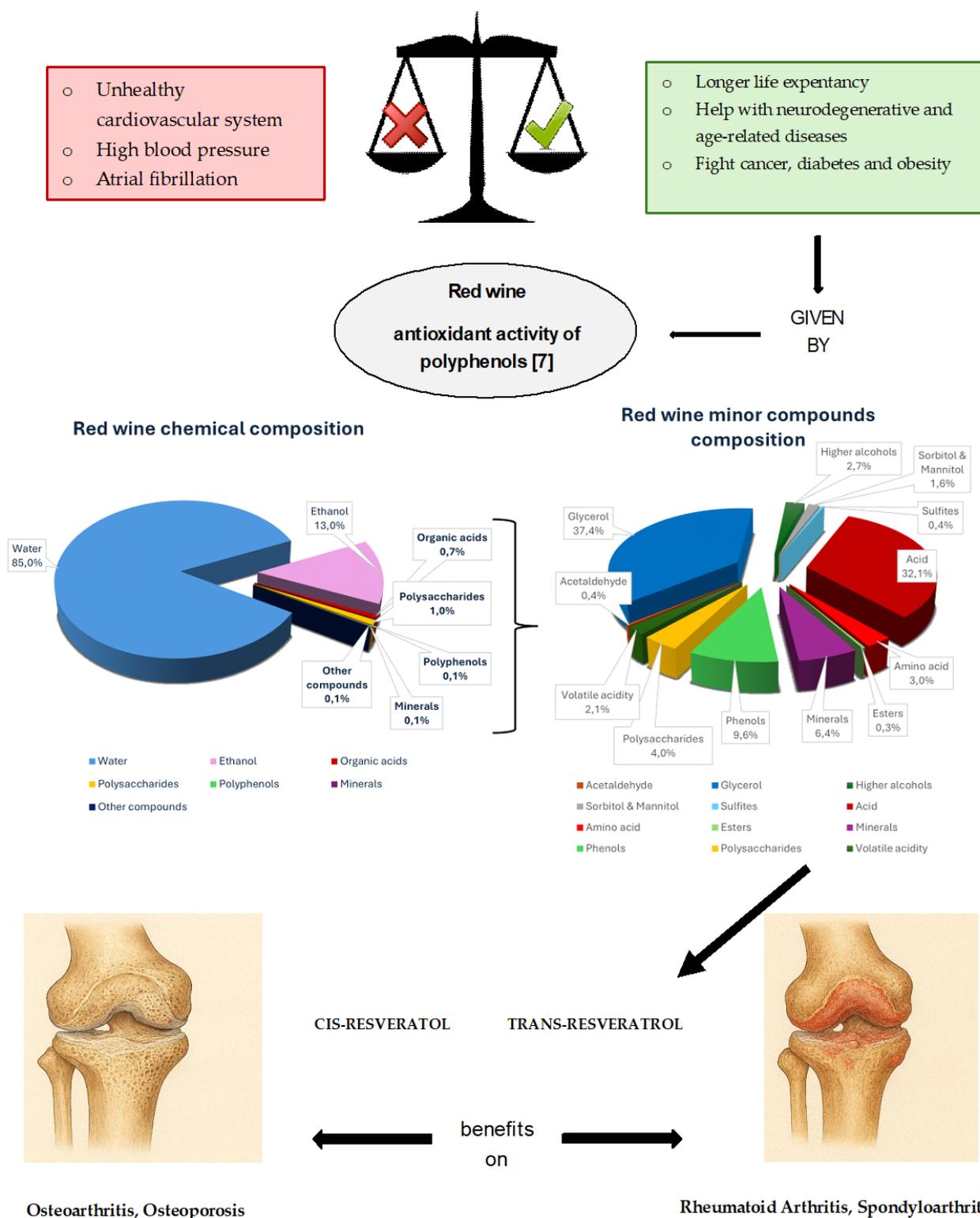Furthermore, it is important to acknowledge that there is no full agreement

Fig. 2. The illustration provides a concise overview of the article, highlighting the chemical composition of red wine (including major and minor compounds) and its potential benefits in addressing various diseases.

within the scientific community regarding the potential risks associated with moderate red wine or alcohol assumption, and future research should focus on optimising administration methods. Otherwise, studies highlight that red wine clones might contain different RS concentrations based on varieties and wine maturity, offering an innovative possibility of research collaboration between medicine and viticulture research areas. Also PTE, a natural misknown compound related to RS with a more persistent body concentration, might have also pivotal promising therapeutic properties.

Furthermore, the possible association with other antioxidant compounds (vita-

min C, vitamin E, curcumin and quercetin) and the innovative strategies such as nanotechnology-based delivery systems, might overcome the low bioavailability of RS that represents a limit for its pharmaceutical use in the next future. Additionally, genetic variations among grapevine clones and techniques such as UV exposure have been shown to enhance RS levels in wine, offering new opportunities to improve the health-related properties of red wine.

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