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REVIEW

Quercetin as an anti-hypertensive: A comprehensive review of the activity of quercetin compounds against Angiotensin Converting Enzyme (ACE) studies

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Abstract

Introduction: Hypertension represents one of the leading global health challenges. The target therapy available for treatment is Angiotensin Converting Enzyme Inhibitors (ACEI). Quercetin is an ACE inhibitor that is used as an anti-hypertensive. **Objective:** This review article aims to study quercetin compounds and their bioactivity as antihypertensives, as well as the development of natural compounds that can be selective against specified target proteins (ACE) and can minimise the possibility of adverse side effects. **Methods:** This study was conducted through a narrative review, collecting journals related to the topics discussed from PubMed, Google Scholar, Scopus, and ScienceDirect, spanning the period from 2010 to 2023. **Results:** Quercetin has the ability to lower blood pressure by forming nitric oxide, which dilates blood vessels. This study also showed that inhibition can affect the activity of angiotensin-converting enzyme (ACE). **Discussion:** According to the study, Quercetin has the potential to have pharmacological activity as an antihypertensive because its binding energy is more negative than the target protein's native ligand (lisinopril). This also indicates that quercetin can form more stable bonds than the standard compound (lisinopril), allowing it to act as an ACE inhibitor. **Conclusion:** Quercetin has potential as an anti-hypertensive with an enzyme-inhibiting mechanism (ACE inhibitor).

Introduction

Hypertension is one of the leading global health challenges. According to data from the World Health Organization (WHO) in 2018, approximately 972 million people worldwide—equivalent to 26.4% of the total population—suffer from hypertension. The prevalence of this condition was recorded at 26.6% among men and 26.1% among women. Due to its rising prevalence, hypertension is considered a significant global health issue. By 2025, it is projected that 1.5 billion individuals will be affected, with an estimated 9.4 million deaths annually attributed to complications related to hypertension.

In Indonesia, the prevalence of hypertension is significantly high, with rates of 29.1% in men and 26.6% in women. According to the 2018 Basic Health Research (Riskesdas) report, hypertension affects 34.1% of individuals aged 18 years and older. The highest prevalence of this condition was observed in South Kalimantan, at 44.1%, while the lowest was recorded in Papua, at 22.2%. When examining prevalence by age, it is clear that the rates increase with age. In the 31-44 age group, the prevalence is 31.6%, rising to 45.3% in the 45-54 age group and reaching 55.2% in the 55-64 age group.

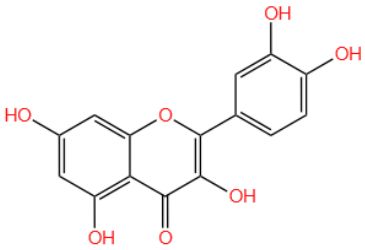
Hypertension arises primarily due to the dysregulation of humoral control mechanisms (Oparil *et al.*, 2018), which is worsened by increased oxidative stress, the production of endothelin-1 (ET-1), and/or hyperactivation of the renin-angiotensin system (RAS). Hypertension has multiple phases, and its pathogenesis is complex, often overlapping with other cardiovascular and metabolic disorders.

One of the leading causes of hypertension is the Angiotensin-Converting Enzyme (ACE). This enzyme plays a crucial role in converting the inactive peptide angiotensin I into its active form, angiotensin II. This process causes vasoconstriction, which in turn increases blood pressure (Zhuo *et al*., 2013). Additionally, hypertension is linked to elevated levels of Reactive Oxygen Species (ROS) in blood vessels and target organs, including the brain and kidneys. The increased presence of ROS exacerbates vascular dysfunction through inflammation and the formation of positive feedback loops that further contribute to hypertension (Fukai & Ushio-Fukai, 2011).

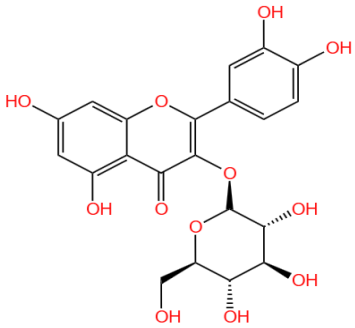
ACE plays a critical role in regulating the RAS by serving as a catalyst that converts angiotensin I to angiotensin II, as well as inactivating bradykinin, a vasodilatory peptide (Gomez *et al*., 2013). ACE inhibition has therefore become a cornerstone of hypertension therapy, providing therapeutic benefits that extend beyond blood pressure regulation (Xie *et al*., 2016). Notably, the discovery that consuming foods rich in flavonols can lower blood pressure has highlighted their potential as natural ACE inhibitors.

Among the various flavonoid subclasses, flavonols (flavan-3-ols) have garnered considerable attention for their cardiovascular benefits (Khan *et al*., 2021). Edible plants rich in flavonols, such as cocoa, tea, and grapes, have been shown in dietary intervention studies to improve vascular function and platelet reactivity in both humans and animals (Grassi *et al*., 2013; West *et al*., 2014; Peluso *et al*., 2015; Ried *et al*., 2017). Regularly consuming foods rich in flavonols—such as cocoa products (de Jesús Romero-Prado *et al*., 2015; Latif & Alsunni, 2016), tea (Hooper *et al*., 2012; Grassi *et al*., 2013; Liu *et al*., 2014), and red wine (Lassaletta *et al*., 2012)—has been linked to significant reductions in blood pressure.

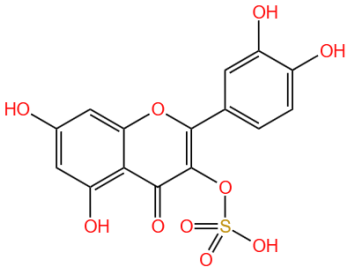
Hypertensive patients are typically managed through pharmacological therapies, including antihypertensive medications tailored to the patient's condition. Angiotensin-converting enzyme inhibitors (ACEIs), such as the synthetic compound lisinopril, are commonly used as second-line treatments. Potential side effects of this therapy can include prolonged cough, dry throat, allergic reactions, dizziness, angioedema, and impaired kidney function (Sousa *et al*., 2016). This has prompted the exploration of natural compounds as alternatives, particularly those targeting ACE with minimal adverse effects. Among the various options, quercetin has emerged as a promising candidate in the development of therapies for hypertension (Figure 1).



Quercetin (1)

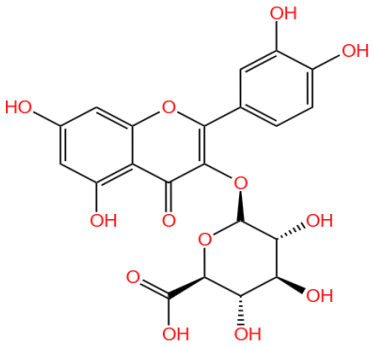


Quercetin glucoside (2)

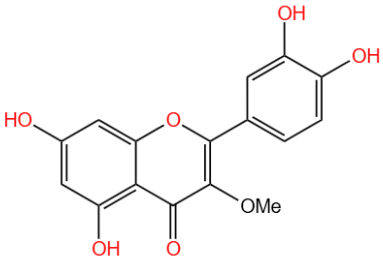


Sulfated quercetin (3)

Figure 1: Structures of quercetin (1) and its metabolites (2-5) (continued)



Glucuronidated quercetin (4)



Methylated quercetin (5)

Figure 1: Structures of quercetin (1) and its metabolites (2-5)

Methods

This study was conducted through a narrative review, collecting journals related to the topics discussed from PubMed, Google Scholar, Scopus, and ScienceDirect, spanning the period from 2010 to 2023, to identify randomised controlled trials examining the activity of quercetin as an antihypertensive agent.

Results

Table I outlines the studies examining metabolites that have been utilised as inhibitors of angiotensin-converting enzyme (ACE).

Table I: Experimental data collection of compounds used as ACE inhibitors

Compounds used	Research from	Experimental media	The most widely used compounds	Reference	Results obtained from the study
Isoflavone compounds, quercetin and captopril	In silico method (molecular docking)	Server pass app	Quercetin	(Nissa *et al.*, 2022)	Quercetin activity as a vasoprotective is higher than that of isoflavone. The results showed that quercetin can bind to ACE, indicating that it has the potential to inhibit ACE and may be used as a therapeutic agent.
Quercetin Lisinopril	In silico	AutoDock Tools 1.5.5 App	Quercetin	(Utari *et al.*, 2021)	Quercetin can potentially exhibit pharmacological activity as an antihypertensive because its binding energy is more negative than that of the target protein's native ligand (lisinopril), allowing it to act as an ACE inhibitor.
Quercetin	In vitro	Male Wistar rats	Quercetin	(Morales-Cano, *et al.*, 2012)	Quercetin has been shown to significantly reduce the increase in right ventricular (RV) weight caused by left ventricular weight plus septum (LV+S) or body weight (BW) in rats with right ventricular hypertrophy. This compound works by causing vasodilation in the pulmonary artery, inhibiting the proliferation of smooth muscle cells, and inducing apoptosis.
Quercetin	In vitro	Adult male spontaneously hypertensive rats	Quercetin	(Monteiro *et al.*, 2012)	Treatment with quercetin for seven days resulted in an average reduction in blood pressure of 10%.
Quercetin	In vitro	Male spontaneously hypertensive rats	Quercetin	(Larson *et al.*, 2012a)	Quercetin significantly reduced arterial blood pressure and heart rate by 14%.
Quercetin	In vitro	587 subjects (299 in the quercetin group; 288 in the control group)	Quercetin	(Serban, *et al.*, 2016)	There is a statistically significant effect of quercetin supplementation in lowering blood pressure, which may be limited to doses above 500 mg per day or even greater.

Discussion

Angiotensin-converting enzyme (ACE) consists of a single polypeptide chain that has two functional domains, namely the N domain and the C domain. Each of these domains contains two catalytic sites. The enzyme is found in its highest concentration in the pulmonary capillaries, but is also present in other tissues, including the proximal tubules of the kidneys, the gastrointestinal tract, the heart, and the brain. ACE exists in two forms: a membrane-bound enzyme and a globular enzyme that circulates in plasma (Balasuriya & Rupasingh, 2011).

ACE inhibitors have a crucial role in reducing systemic vascular resistance and reducing mean diastolic and systolic blood pressure in various hypertensive conditions. Experimental studies conducted in animal models of renal hypertension or genetic hypertension have demonstrated the effectiveness of ACE inhibitors in lowering blood pressure, except in cases associated with primary aldosteronism. The mechanism through which quercetin acts as an ACE inhibitor is illustrated in Figure 2.

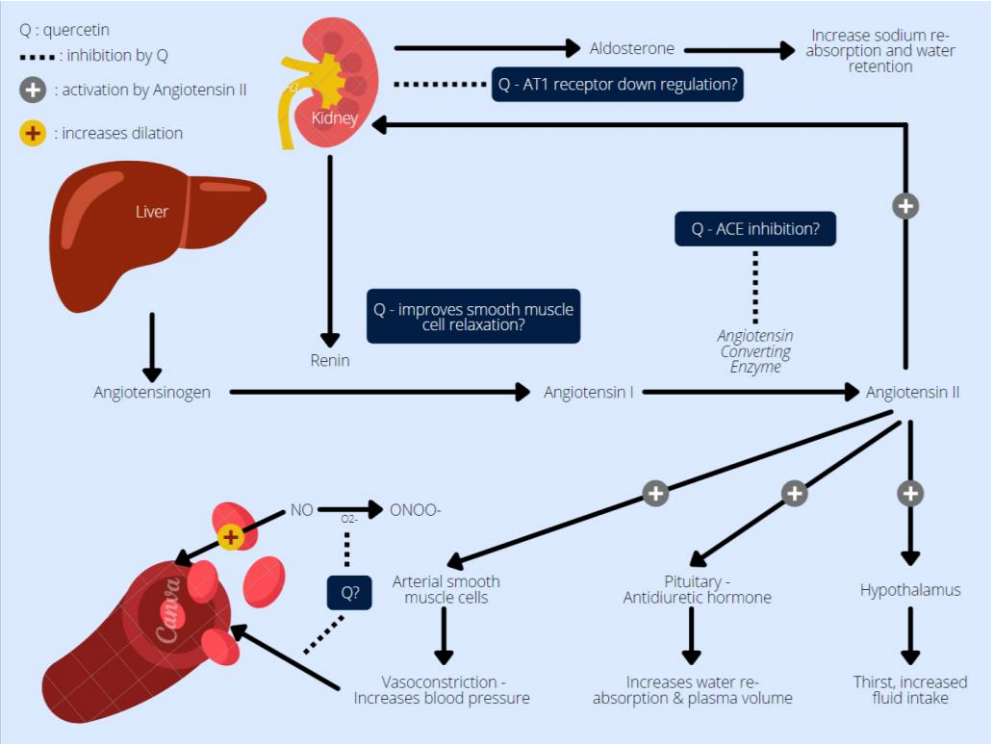


Figure 2: Mechanism of quercetin as an ACE inhibitor

ACE is a pivotal enzyme in blood pressure regulation, producing angiotensin II, a key compound that promotes vasoconstriction. In hypertensive individuals, angiotensin II levels are elevated. A reduction in angiotensin II levels is associated with a decrease in blood pressure. This understanding forms the theoretical foundation for the development of ACE-inhibiting drugs, which function by binding to the active site of ACE, thereby blocking the conversion of angiotensin I into angiotensin II (Herman *et al*., 2023).

Quercetin's ability to reduce oxidative stress is associated with its blood pressure-lowering effects. Animal studies have revealed reductions in blood pressure following quercetin supplementation, accompanied by improvements in oxidative status. This study demonstrated a decrease in plasma lipid peroxide levels (Ciocoiu *et al*., 2013; Wang *et al*., 2013; Vrolijk *et al*., 2020) and urinary isoprostanes (Vrolijk *et al*., 2020) compared to a control group that did not receive treatment. The observed improvement in oxidative status is believed to be the underlying cause of the enhanced vascular function observed in this study (Ciocoiu *et al*., 2013; Wang *et al*., 2013; Vrolijk *et al*., 2020).

Research by Utari *et al*. (2021) demonstrated that lisinopril, a well-established ACE inhibitor, exhibited a root mean square deviation (RMSD) value of 2.86 and a binding energy of - 4.66 kcal/mol when interacting with

ACE. Visualisation of the interaction shows the presence of hydrogen bonds between the amino acid residue GLY2000 in the protein and the native ligand. This bond involves the HN3 group of the protein and the O4 atom of the ligand.

Quercetin's interaction with ACE displayed a binding energy of -6.32 kcal/mol, indicating a stronger bond than that of lisinopril. Lower binding energy signifies stronger interactions, suggesting that quercetin forms a more stable complex with ACE than the standard compound (lisinopril). These findings support the pharmacological potential of quercetin as an antihypertensive agent. Further evidence was provided by Muhammad & Nighat (2015), who demonstrated that quercetin's binding to ACE was more stable than that of the standard compound.

Structurally, ACE's N- and C-domains differ in their catalytic efficiency. For example, the C domain hydrolyses hippuryl-histidyl-l-leucine (H-HL) nine times faster than the N domain. However, the C and N domains hydrolyse N-benzyloxycarbonyl-l-phenyl-alanyl-l-histidyl-l-leucine (Z-FHL) at the same rate. Conversely, inhibition of angiotensin-converting enzyme (ACE) reduces the production of angiotensin II, leading to vasodilation and a decrease in blood pressure. This is a common way to use ACE inhibitors in the treatment of hypertension.

The renin-angiotensin system (RAS) (Figure 3) plays a crucial role in regulating blood pressure and maintaining fluid homeostasis. Pharmacological ACE inhibitors interfere with RAS by reducing circulating angiotensin II levels, thereby alleviating vasoconstriction and lowering blood pressure. This, in turn, decreases cardiovascular risks in high-risk populations (Weiss *et al*., 2013; Messerli *et al*., 2018). This inhibitor works by inactivating ACE by binding to the zinc-containing active site. This stops the conversion of angiotensin I to angiotensin II. Quercetin's ability to bind to zinc molecules suggests the mechanism behind its ACE inhibitory activity (Daskaya-Dikmen *et al*., 2017).

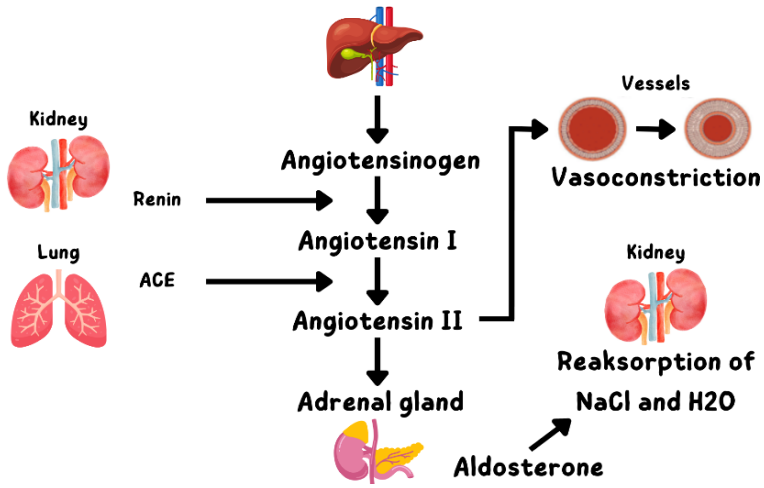


Figure 3: The renin-angiotensin system (RAS)

Quercetin, a phenolic compound, exhibits a strong ability to bind Angiotensin-Converting Enzyme (ACE) and acts as an effective vasodilator and vasoprotector. This makes quercetin a potential candidate for use as an ACE inhibitor and antihypertensive drug. Consistent with this, research by Novita (2016) highlighted quercetin's ability to lower blood pressure by inhibiting the ACE enzyme, reinforcing its potential as an antihypertensive agent (Oparil *et al*., 2018). Similarly, Widiasari's 2015 study demonstrated that quercetin derived from soybean tempeh could reduce blood pressure through in vitro inhibition of ACE activity (Widiasari, 2018).

Additionally, studies indicate that Capers possess significant ethnomedicinal applications in hypertension management due to quercetin's role in forming nitric oxide, a compound essential for blood vessel dilation. However, quercetin's bioavailability depends on its absorption and metabolism, which vary based on its chemical form (e.g., quercetin aglycone or glycosides), the food matrix in which it is contained, and individual differences in gut microbiota (Kaushik *et al*., 2012; Kashino *et al*., 2015; Maciej *et al*., 2015; Burak *et al*., 2017; Kay *et al*., 2017; Somerville *et al*., 2017; Vitale *et al*., 2018; Dabeek & Marra, 2019; Muñoz-Reyes *et al*., 2021).

Quercetin (3,3',4',5,7-pentahydroxyflavone), depicted in Figure 1, is a flavonol-type flavonoid commonly found in a variety of fruits and vegetables, including berries, tea, apples, and onions (Table II). It is known for its antioxidant, anti-inflammatory, and vascular dilation properties. It also has potential as an anticancer agent (Williamson *et al*., 2018). Structure-activity relationship analyses indicate that quercetin's physical properties are influenced by its chemical structure, allowing it to chelate metals and affect metal ion transport, bioavailability, and toxicity. Three distinct chelating sites in its molecular structure enable such interactions, classified as catechol, Nα-hydroxycarbonyl, and Nβ-hydroxycarbonyl (Ravichandran *et al*., 2014).

Table II: Content of quercetin in natural compounds, adapted from the literature database

Natural compounds	Methods	Quercetin content	Reference
Capers	HPLC analysis	The hydroalcoholic fraction contains the highest level of Quercetin, reaching 7.415 ± 0.405 mg/g. Furthermore, the chloroform fraction recorded a content of 4.986 ± 0.309 mg/g, followed by the ethyl acetate fraction, which has a content of 2.897 ± 0.312 mg/g	(Kalantari *et al*., 2017)
Onion leaves	HPLC analysis	1497.5 mg/kg	(Kafoud *et al*., 2023)
Black tea	HPLC analysis	1070.0 mg/kg	(Kafoud *et al*., 2023)
Cocoa powder	LC-MS	2.10–40.33 µg/g	(Younes *et al*., 2023)
Lingonberry	RP-HPLC	74 and 146 mg/kg	(Häkkinen *et al*., 1999)
Chokeberry	RP-HPLC	89 mg/kg	(Häkkinen *et al*., 1999)
Apple	HPLC analysis	236.60 ± 3.12 mg/100 g	(Ponder *et al*., *et al*., 2022)

Capparis aphylla

In anesthetised rats with normotensive blood pressure, intravenous administration of quercetin extracted from *Capparis aphylla* (Ca.Cr) caused a decrease in mean arterial pressure (MAP) by 12–39%. Research conducted by Abdul (2010) demonstrated that the crude extract of Capparis aphylla inhibited the movement of calcium ions (Ca^{2+}) through both receptor-operated Ca^{2+} channels and voltage-dependent Ca^{2+} channels (VDCC). This finding was supported by a rightward shift in the Ca^{2+} concentration-response curve in rabbit aortic tissue previously treated with the crude extract and its fractions. In addition, studies using isolated rat aortic rings indicated that Ca.Cr was able to induce vasodilation through mechanisms that were partly endothelium-dependent and partly endothelium-independent.

Allium fistulosum

Research conducted by Țigu in 2021 demonstrated that high concentrations of Allium fistulosum L. extract can impact the growth of human fibroblasts and keratinocytes, with effects varying according to the dose used. Morphological changes observed via triple staining indicated cellular death primarily through necrosis, as confirmed by flow cytometry and analyses of Casp3, LDH, and CAT activity (Tigu *et al*., 2021).

Camellia sinensis

In a study investigating the antihypertensive effects of GTF, OTF, and BTF extracts for 24 hours, it was found that BTF extract lowered systolic blood pressure (SBP) and diastolic blood pressure (DBP) by a significant reduction rate of 57.08 mmHg and 64.33 mmHg, respectively, within eight hours, even greater than captopril. This antihypertensive works together with ACE inhibitors (Mahdavi-Roshan *et al*., 2020).

Theobroma cacao

Asiedu-Gyekye's 2016 study demonstrated that quercetin strongly inhibits HCA enzymatic activity, with an efficacy 25 and 96 times greater than CLT and CLP, respectively. Procyanidins, a significant component of cocoa liquor polyphenols, are believed to contribute significantly to these effects through their antimutagenic mechanisms (Asiedu-Gyekye *et al*., 2016).

Vaccinium Vitis-idea

Meta-analyses of cranberry supplementation revealed a modest reduction in systolic blood pressure (SBP) by - 3.63 mmHg (95% CI: - 6.27, - 0.98) without a significant effect on diastolic blood pressure (DBP). Stratified analyses suggested a more pronounced SBP reduction in participants under 50 years old (- 6.26 mmHg, 95% CI: - 10.73, - 1.79) compared to older age groups.

Quercetin, abundant in cranberries, likely contributes to these effects by reducing oxidative stress, improving endothelial function, and inhibiting ACE (Tom *et al*., 2010; Larson *et al*., 2012b; Harding *et al*., 2012; Monteiro *et al*., 2012; Friedenreich *et al*., 2013; Palanisamy & Venkataraman, 2013; Pruijm *et al*., 2013; Li *et al*., 2016; Weh *et al*., 2016; D'Elia, 2018; Soares *et al*., 2019; Amadi *et al*., 2020).

Aronia melanocarpa

Ciocoiu's 2013 study highlighted the potential of black chokeberry (Aronia melanocarpa) extract as both a prophylactic agent and a nutritional supplement for managing hypertension. Its polyphenolic compounds prevent oxidative stress and maintain antioxidant capacity, although additional research is needed to understand the cellular and molecular mechanisms underlying these effects fully (Ciocoiu *et al*., 2013).

Malus

Various metabolites of quercetin found in humans, such as quercetin-3-O-glucuronic acid, quercetin-3-O-sulfate, and isorhamnetin-3-O-glucuronic acid, have been studied for their ACE inhibitory activity. Based on a study conducted by Nileeka (2012), quercetin-3-O-glucuronic acid showed the lowest IC50 value, indicating significant ACE inhibition and a potential role in modulating the renin-angiotensin-aldosterone system (RAAS) (Balasuriya & Rupasinghe, 2012; Wick *et al*., 2016). In addition, quercetin has also been shown to reduce plasma extravasation by inhibiting ACE and endopeptidase, further supporting its ability to lower blood pressure (Wick *et al*., 2016).

Conclusion

The quercetin compound exhibits affinity for the angiotensin-converting enzyme (ACE), its target protein. This indicates that quercetin has the potential as an antihypertensive agent through its mechanism of action as an enzyme inhibitor (ACE inhibitor). Thus, it is hoped that in the future, quercetin can be applied as a preventive and adjuvant therapy for hypertension sufferers.

Conflict of Interest

The authors declare that they have no conflict of interest.

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