VER
Vascular & Endovascular Review

Capsaicinoids and Piperine in Cardiovascular Physiology: Autonomic, Endothelial, and Myocardial Pathways

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ABSTRACT

Pepper-derived phytochemicals, particularly volatile terpenoids and pungent alkaloids from Capsicum and Piper species, have attracted increasing attention for their complex cardiovascular effects. Bioactive constituents such as capsaicinoids and piperine interact with transient receptor potential vanilloid 1 (TRPV1) channels, autonomic regulatory circuits, endothelial function, and myocardial signalling pathways, suggesting both cardioprotective potential and cardiovascular risk. This review critically synthesises current experimental, clinical, and epidemiological evidence concerning the cardiovascular actions of pepper-related volatile oils, with particular emphasis on their role in typical and atypical cardiac pain.

Preclinical studies consistently demonstrate TRPV1-mediated mechanisms that may promote cardioprotection, including improved endothelial function, modulation of ischemic injury, and attenuation of adverse myocardial remodelling. In contrast, concentrated or non-dietary exposures have been associated with adverse cardiovascular effects, such as sympathetic activation, coronary vasospasm, and arrhythmogenic potential. Human evidence remains inconclusive. Case reports describe acute cardiac events following high-dose exposure to capsaicinoids or piperine-containing products, whereas population-based studies generally associate habitual dietary intake of peppers with favourable cardiovascular outcomes. Despite limited clinical validation, piperine has emerged as a promising candidate due to its anti-inflammatory, antioxidant, and metabolic effects observed in experimental models.

By integrating mechanistic, translational, and clinical findings, this review highlights critical gaps in current knowledge, including the scarcity of controlled human trials, incomplete pharmacokinetic and pharmacodynamic characterisation, and the absence of systematic surveillance of adverse cardiovascular events. Finally, key priorities for future research are proposed to clarify the therapeutic potential and safety profile of pepper-derived phytochemicals in cardiovascular health and disease.

KEYWORDS: Capsicum; Piperine; Capsaicin; Volatile oils; TRPV1; Cardiovascular physiology; Chest pain; Coronary vasospasm; Cardioprotection; Pepper-induced cardiac effects; Atypical cardiac pain; Phytochemicals; Autonomic modulation; Ischemic preconditioning; Cardiovascular risk..

How to Cite: Asha M P, Raji Rajan, Justin R Nayagam, (2025) Capsaicinoids and Piperine in Cardiovascular Physiology: Autonomic, Endothelial, and Myocardial Pathways, Vascular and Endovascular Review, Vol.8, No.3, 181-189

INTRODUCTION

Phytochemicals derived from peppers, particularly species of Capsicum sp. and Piper sp., have long attracted scientific interest because of their diverse bioactivity and widespread use in diets, traditional medicines, and commercial supplements. These plants are rich sources of volatile terpenoids and pungent alkaloids, most notably capsaicinoids in Capsicum species and piperine in Piper species. Beyond their characteristic sensory properties, these compounds exert pleiotropic biological effects, and an expanding body of evidence suggests that they influence multiple physiological pathways relevant to cardiovascular function (Munjuluri et al., 2021; Yamani et al., 2021).

One of the principal molecular targets of pepper-derived bioactives is the transient receptor potential vanilloid 1 (TRPV1) channel. TRPV1 is predominantly expressed in sensory neurons but is also present in vascular smooth muscle cells and endothelial cells. Activation of TRPV1 by capsaicin promotes calcium influx, leading to the release of vasoactive mediators such as neuropeptides and nitric oxide. Although the precise mechanisms remain incompletely defined, TRPV1 activation has been implicated in vasodilatory responses and broader cardiovascular effects. Preclinical studies suggest that capsaicin-mediated TRPV1 signalling may confer cardioprotection by improving endothelial function, reducing oxidative stress, enhancing metabolic efficiency, and promoting ischemic preconditioning (Munjuluri et al., 2021; Zhang et al., 2016). Experimental models further indicate that capsaicin exposure prior to ischemia–reperfusion injury may lower blood pressure, improve coronary perfusion, and reduce myocardial injury (Zhang et al., 2016; Li et al., 2021).

Epidemiological evidence generally aligns with these experimental findings. A recent meta-analysis of prospective cohort studies encompassing over 560,000 participants reported a significantly lower risk of all-cause and cardiovascular mortality among habitual consumers of chilli peppers compared with infrequent or non-consumers (Shi et al., 2021; Yamani et al., 2021). These observations raise the possibility that sustained low-level dietary exposure to pepper-derived bioactives may exert population-wide cardioprotective effects.

However, emerging data also indicate potential cardiovascular risks associated with high-dose or non-dietary exposures. Case reports and mechanistic studies suggest that excessive activation of TRPV1—particularly through supplements or topical formulations—may promote sympathetic activation, coronary vasoconstriction, and ischemia, especially in individuals with pre-existing cardiovascular disease (Munjuluri et al., 2021; Zhang et al., 2016). These contrasting effects underscore the importance of dose, route of exposure, and individual susceptibility, factors that are inconsistently addressed across existing studies.

Notably, there remains a paucity of controlled clinical trials examining the cardiovascular consequences of pepper-derived compounds, particularly with respect to coronary function, chest pain (both typical and atypical), and long-term cardiovascular safety. Variability in exposure type, dosage, and host factors further complicates interpretation of the available evidence (Shi et al., 2021; Yamani et al., 2021).

In light of these considerations, this review aims to critically evaluate the dual cardiovascular actions of pepper-derived volatile and pungent phytochemicals. Specifically, it will: (a) characterise key bioactive constituents; (b) synthesise mechanistic and preclinical evidence relevant to vascular and myocardial physiology; (c) summarise epidemiological and clinical findings linking pepper exposure to cardiac pain and cardiovascular events; (d) assess methodological limitations and sources of bias; (e) identify major knowledge gaps; and (f) propose priorities for future research. By integrating mechanistic, translational, and clinical data, this review seeks to clarify the conditions under which pepper-derived phytochemicals may be cardioprotective or harmful, and to inform safer dietary and therapeutic use.

PHYTOCHEMISTRY OF PEPPER AND CHILLI VOLATILE OILS

2.1 Capsaicinoids (Capsicum spp.)

The capsaicinoids in Capsicum fruits comprise a wide variety of compounds, with capsaicin and dihydrocapsaicin constituting approximately 80 - 90% of the total capsaicinoid pungency. The chemical formula for capsaicin is trans 8-methyl-N-vanillyl-6 nonenamide. Capsaicin is the primary and best-studied capsaicinoid; it produces sensory irritation from both peripheral and central neuronal hypersensitivity, and these effects are mediated by the activation of the TRPV1 receptor. TRPV1 is an ion channel expressed on the surface of C-fibres, endothelial cells, smooth muscle cells and cardiomyocytes. Upon activation by capsaicin binding, TRPV1 opens (>10-fold), allowing for the immediate influx of calcium ions (Ca^{2+}), which causes the release of calcitonin gene-related peptide (CGRP) and substance P, two neuropeptides involved in vasodilation, nociceptive transmission and autonomic mediation. CGRP promotes vasodilation via NO, reducing vascular resistance and improving microcirculation during ischemic stress. Studies in animals show that there may be some protective effect of chronic, low-dose stimulation of TRPV1 on the heart by decreasing infarct size from ischaemia-reperfusion due to enhanced mitochondrial health and reductions in inflammation (Sun et al., 2019).

Capsaicinoids exhibit antioxidant and anti-inflammatory effects, such as inhibiting NF-kB, decreasing reactive oxygen species, and modulating PPAR pathways, thus helping to alleviate endothelial dysfunction, decrease inflammation that contributes to angina, and correct autonomic imbalances resulting in atypical cardiac pain (Barbero & Liazid, 2019). The essential oil portion of Capsicum contains terpenes (limonene, β-caryophyllene, linalool, α-pinene, and β-myrcene), all of which have individual actions on the cardiovascular system, such as causing vasodilation by relaxing smooth muscle, providing anti-inflammatory effects through the activation of CB2 receptors, stimulating the parasympathetic nervous system, and modulating autonomic activity. Together, these terpenes may work synergistically with capsaicinoids to enhance the cardiovascular effects and balance out the autonomic effects of each other. At common consumption levels, capsaicin generally has a cardio-protective effect by improving endothelial function, enhancing coronary microvascular perfusion, producing a protective effect similar to preconditioning of the myocardium, and decreasing sympathetic dominance, thus having the potential to lessen atypical chest pain. High dosing (either aerosolized or in concentrated extract) can cause deleterious effects such as causing profound sympathetic activation leading to tachycardia (rapid heartbeat) and hypertension, vasospasm of coronary arteries, causing esophageal or chest wall discomfort mimicking atypical angina, and ST-segment changes, as in the case of pepper spray exposure (Chin et al., 2020; Sun et al., 2019). The presence of both positive and negative effects of capsaicinoids illustrates the need to evaluate capsaicinoids relative to cardiovascular health based on both dose and route of exposure.

2.2 Piperine and Piper Species

Black pepper (Piper nigrum) and other species of the Piper family also contain Piperine. Minor amounts of Chavicine, Sabinene and Pinene are present when piperine is consumed. Piperine is studied in the following areas related to Cardiovascular Diseases: Antioxidants, Anti-inflammatory Effects, and Endothelial Protectors. The Cardiovascular Disease Anti-phenomenon includes Modulative Effects through NF-κB, Nrf2, and Calcium handling pathways (Dulate et al., 2020). Animal studies show that Piperine can: reduce oxidative stress; prevent lipid peroxidation; and Increase Nitric Oxide Bioavailability, improving Endothelial Function, leading to vascular homeostasis and possible Cardioprotection. In Research Models, Piperine has also exhibited mild negative chronotropic Black pepper (Piper nigrum) and other species of the Piper family also contain Piperine. Minor amounts of Chavicine, Sabinene and Pinene are present when piperine is consumed. Piperine is studied in the following areas related to Cardiovascular Diseases: Antioxidants, Anti-inflammatory Effects, and Endothelial Protectors. The Cardiovascular Disease Anti-phenomenon includes Modulative Effects through NF-κB, Nrf2, and Calcium handling pathways (Dulate et al., 2020). Animal studies show that Piperine can reduce oxidative Stress; prevent lipid peroxidation; and Increase Nitric Oxide Bioavailability, improving Endothelial Function, leading to vascular homeostasis and possible Cardioprotection. In Research Models, Piperine has also exhibited mild negative chronotropic (slowing of heart rate) and inotropic (reduction in force of contraction) effects, indicating its ability to modulate cardiac autonomic tone (Reddy & Srinivasan, 2019). These findings indicate that Piperine could be an effective Agent for reducing Endothelial Dysfunction and Inflammation related to Ischemic or Non-Ischemic Cardiac Types of Pain. However, there is currently limited Clinical Validation of these findings and further evaluation is needed to determine

Specific Dose-Response Relationships related to Cardiovascular Benefits of Piperine. (Reddy & Srinivasan, 2019). These findings indicate that Piperine could be an effective Agent for reducing Endothelial Dysfunction and Inflammation related to Ischemic or Non-Ischemic Cardiac Types of Pain. However, there is currently limited Clinical Validation of these findings and further evaluation is needed to determine Specific Dose-Response Relationships related to Cardiovascular Benefits of Piperine.

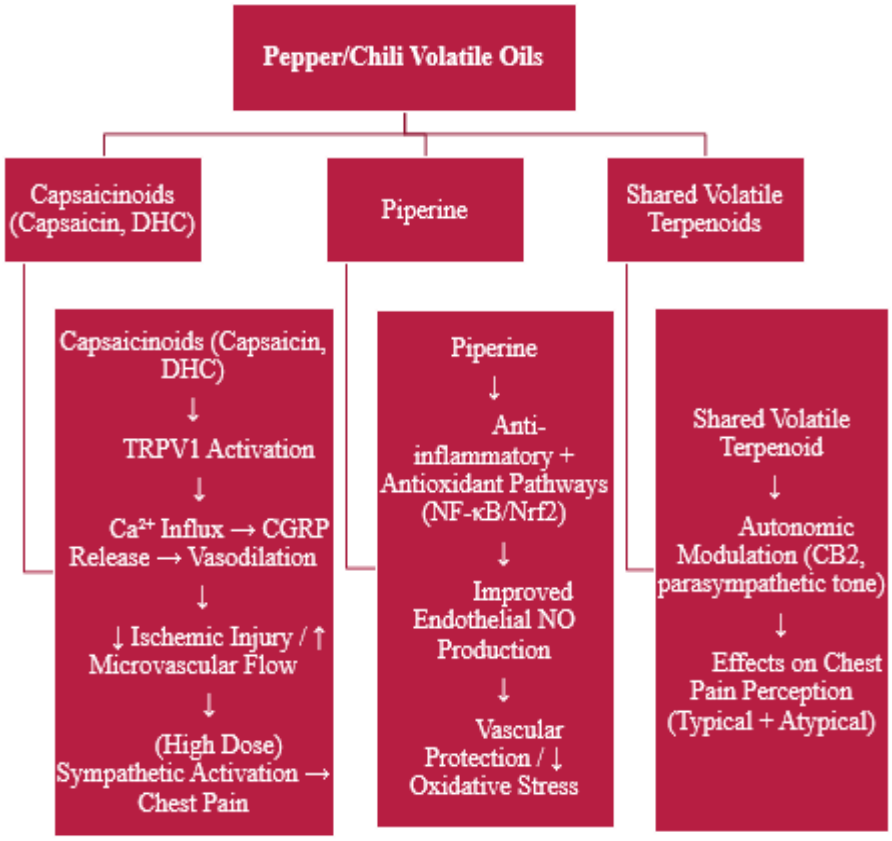
2.3 Volatile Terpenoids Shared Across Pepper and Chilli Species

In addition, both Capsicum and Piper species contain numerous volatile terpenoids, including α-pinene, β-pinene, β-caryophyllene, limonene, linalool and β-myrcene, all of which have been found to exert cardiovascular and autonomic effects independently of each other. For example, β-caryophyllene acts as an agonist to the cannabis CB2 receptor, which reduces vascular inflammation and oxidative stress. Likewise, limonene is known to have parasympathomimetic and anti-inflammatory properties, supporting the autonomic balance and microvascular function (Gertsch et al., 2008; Sun, 2019). Additionally, Pinene isomers exert effects related to bronchodilatory activity and modulation of autonomic tone, which may affect both heart-rate variability and how atypical chest discomfort is interpreted (Salehi et al., 2019). These three families of terpenoids may work synergistically with capsaicin and Piperine to create greater vasodilation, endothelial function, and sympathetic-parasympathetic balance than either terpenoid or capsaicin alone. Ultimately, alkaloids and volatile terpenoids in pepper and chilli are part of a complex phytochemical network with both cardioprotective and potentially adverse effects, thereby requiring an assessment of all factors, including dose, route of exposure, and individual cardiovascular risk, to determine their complete impact.

Table 1. Major Phytochemicals in Capsicum and Piper Species and Their Cardiovascular Actions

Compound/Class	Source	Mechanisms	Cardiovascular Effects	References
Capsaicin	Capsicum spp.	TRPV1 activation → Ca^{2+} influx → CGRP release	Vasodilation, ischemic protection; high-dose sympathetic activation	Zhang & Li, 2016; Sun et al., 2019
Dihydrocapsaicin	Capsicum spp.	Similar to capsaicin	Vasodilation, metabolic modulation	Barbero & Liazid, 2019
Piperine	Piper spp.	NF-κB inhibition, antioxidant pathways	Anti-inflammatory, endothelial protection, mild chronotropic suppression	Dulate et al., 2020; Reddy & Srinivasan, 2019
β-Caryophyllene	Both	CB2 agonism	Anti-inflammatory, vascular protection	Gertsch et al., 2008
Limonene	Both	Anti-inflammatory; parasympathomimetic	Reduced autonomic stress; improved vascular tone	Sun, 2019
Pinene	Both	Autonomic and respiratory modulation	Bronchodilation, autonomic balance	Salehi et al., 2019

Fig 1.Cardiovascular Pathways Influenced by Pepper-Derived Volatile Oils



MECHANISTIC BASIS OF CARDIOVASCULAR EFFECTS

Cardiovascular responses to the pungent alkaloids and volatile oils of peppers are the result of both integrated molecular receptor signalling, endothelial and smooth muscle function, and autonomic reflexes that act throughout the cardiovascular system via various myocardial cellular pathways. The summary below elaborates on the basic pathways by which the above pathways produce or prevent each specific type of cardiac pain (e.g., typical myocardial ischemic cardiac pain versus atypical or neurogenic vasospastic cardiac pain) through the involvement of TRPV1 signalling, autonomic modulation, vascular reactivity and cardiomyocyte pathways; as described below for each example of types of cardiac pain.

3.1 TRPV1 activation and cardioprotection

Transient receptor potential vanilloid channel 1 (TRPV1) is a non-selective cation channel that is highly Ca^{2+} permeable. TRPV1 is located on sensory C-fibres that supply nerves in both the heart and vasculature, on vascular endothelial cells, less so on vascular muscle and on cardiomyocytes (New Phytol, 2016; Munjuluri et al., 2021). The activation of TRPV1 due to capsaicin or a related agonist leads to a rapid influx of Ca^{2+}, which causes sensory neuropeptides to be released, most notably calcitonin gene-related peptide (CGRP) and substance P. CGRP is a powerful vasodilator that works through mechanisms involving the vascular endothelium and smooth muscle by stimulating the synthesis of nitric oxide (NO) and cyclic GMP pathway, decreasing vascular resistance, and improving microvascular blood perfusion. The TRPV1→CGRP→NO pathway is responsible for many of the cardioprotective effects seen in preclinical studies. Activation of TRPV1 at low doses, or repeatedly, has produced ischemic preconditioning-like effects by decreasing infarct size resulting from ischemic/reperfusion injuries, stabilising mitochondrial function, and decreasing release of the pro-inflammatory cytokine (Zhang & Li, 2016; Munjuluri et al., 2021). In a few electrophysiological studies, researchers reported a decrease in the vulnerability of arrhythmia due to ischemia as a result of TRPV1 activation (due to improved perfusion and reduced oxidative stress). However, it is important to note that TRPV1 signalling is not linear; changes in desensitisation of the receptors, different levels of receptor expression, and co-existing inflammation can all create variations in their overall effect.

3.2 Autonomic modulation

Pepper bioactives can cause dose and route-dependent autonomic changes and directly influence the cardiac system through dose and route dependency. Capsaicin's low doses in humans or animals through oral administration before moderate dosing have been shown to increase parasympathetic predominance, decrease HR at rest and increase HR variability indices, which could be cardioprotective over the course of prolonged exposures. In contrast, acute exposures to high doses of capsaicin, ranging from inhalation of aerosolised capsaicinoids, ingestion of concentrated capsaicin supplements, or dermally administered in such a manner to allow entry of higher systemic quantities into the body, have been noted to produce acute sympathetic stimulation with tachycardia, hypertension and increased myocardial oxygen demand (Sogut and colleagues 2012).

In addition, acute exposure to capsaicin can activate airway and skin pain receptors, causing reflex activation of the sympathetic nervous system and release of the neuropeptides throughout the body, creating a systemic disturbance in vascular tone. This disturbance could contribute to two mechanisms in producing chest discomfort: the first is demand ischemia due to increased myocardial oxygen requirements, while the second could include chest discomfort as a result of increased vagal activity, as well as stimulation of the vagus nerve due to reflex sympathetic activation, creating sensations within the chest area. Implications for practice: When considering the differential diagnosis of acute chest pain associated with exposure to pepper, physicians should evaluate both mechanisms of demand-induced ischemia and neurogenic/autonomic activation (non-ischemic chest pain).

3.3 Vascular effects — concentration and context matter

Capsaicinoids and terpenes have varied vascular effects that are largely determined by the concentration and context in which they are administered. At lower doses, the effects of TRPV1-mediated CGRP release and direct relaxation of vascular smooth muscle cells (via specific terpenes, such as limonene and myrcene) lead to overall vasodilation (greater blood flow), improved endothelial function and increased microcirculation. These various mechanisms of action can decrease the amount of work the heart has to perform and potentially decrease the ischemic condition in sensitive tissue beds.

However, under some circumstances, especially when large amounts of these substances are present in one local region, and/or there is dysfunction of the endothelial layer and/or when there is an inflammatory priming effect associated with them, the result can change from vasodilation to vasoconstriction or vasospasm. The proposed mechanisms for the development of a vasospasm following the use of capsaicin or terpenoids can include sympathetic reflexes (mediated through activation of TRPV1), excess stimulation (i.e., increased excitability) of smooth muscle cells, through altered calcium handling and an imbalance between vasodilators (CGRP and nitrous oxide) and vasoconstrictors. There are past case reports of vasospasms resulting in ST-segment changes on a 12-lead electrocardiogram following the application of high-concentration capsaicin or pepper-spray (Munjuluri et al., 2021; Chin et al., 2020).

3.4 Myocardial cellular pathways

Pepper-related compounds have an impact on the way heart cells grow and live by affecting how their cells communicate with each other about inflammation. One way that these compounds affect survival is by activating a common pathway called the PI3K/Akt pathway. Studies on animals show that activation of the PI3K/Akt pathway is linked to increased survival after the heart experiences an ischemic event (when blood flow to the heart stops), and helps protect the mitochondria, which keeps them functioning properly and helps reduce apoptosis (death of heart cells). Another way that capsaicin and piperine help protect the heart is by acting as antioxidants and reducing the amount of lipid peroxidation products generated during the inflammatory response that causes ischemia or reperfusion injury. Studies on capsaicin and piperine show that these compounds suppress the activation of NF-κB, leading to decreased production of cytokines, a substance associated with the inflammatory response that

can lead to atherothrombotic events. Consequently, the effects of capsaicin and piperine on intracellular signalling pathways may, in part, explain the reduced size of myocardial infarctions and remodelling effect seen in numerous investigations involving rodents. However, there are significant differences in pharmacokinetics, timing, and dosage between most of the studies in animals to translate these findings into humans; careful research to determine the best dosages and times for humans will be needed before clinical use of capsaicin or piperine in patients with heart failure can be established.

The connection between biological systems (spicy ingredients) and cardioprotection through the TRPV1/CGRP/NO pathway, as well as with cardiovascular disease through sympathetic surges, vasospasm and or high concentrations of Spicy bioactives in specific settings, is readily apparent when looking at the mechanistic data. The dose of the specific bioactive, the way it is administered and the condition of the endothelial system, as well as the responsiveness of the autonomic system, determine whether the net clinical outcome from a combination of the mechanisms/paths is positive (therapeutic) or negative (harmful) for each patient. There is therefore an urgent need for precisely designed clinical studies in humans examining the interaction of the bioactives on human physiology, and the accurate pharmacokinetic and pharmacodynamic profiles for these agents in humans, in order to accurately identify safe therapeutic ranges.

Table 2. Cellular sites of TRPV1 expression and principal cardiovascular consequences of activation

Cell / Tissue	TRPV1 role / response to activation	Cardiovascular consequence	references
Sensory C-fibers (cardiac & vascular)	Ca^{2+} influx → CGRP / substance P release	Vasodilation, neurogenic inflammation, altered nociception (atypical pain)	Zhang & Li, 2016; Munjuluri et al., 2021
Vascular endothelium	Endothelial NO release (indirect via CGRP / direct Ca^{2+})	Endothelium-dependent vasodilation, improved microcirculation	Zhang & Li, 2016
Vascular smooth muscle	Modulation of Ca^{2+} handling	Dose-dependent vasodilation or vasoconstriction (vasospasm risk)	Munjuluri et al., 2021
Cardiomyocytes	Activation of survival pathways (PI3K/Akt), reduced ROS	Reduced infarct size, improved post-ischemic recovery (preclinical)	Li et al., 2021

TYPICAL CARDIAC PAIN (ISCHEMIC CHEST PAIN): EVIDENCE REVIEW

4.1 Protective effects (experimental and epidemiological)

4.1.1 Preclinical models

Preclinical models in animals and cells provide substantial evidence that capsicum/capsaicin and constituent compounds exhibit protective properties in the cardiovascular system. Studies with rodents that are subjected to ischemia-reperfusion (I-R), and where animals are pretreated with capsicum/capsaicin/capsaicin-acicular extracts before I-R, have consistently yielded a significant reduction in infarct size, improved recovery from I-R Injury, and were associated with improvements in myocyte function in the post-I-R phase. Studies suggest that the protective effects of capsicum/capsaicin are mediated via the TRPV1 (transient receptor potential vanilloid potential channel subtype 1) system. TRPV1 has been shown to stimulate the release of sensory neuropeptide CGRP (calcitonin gene-related peptide), enhance endothelial NO production and signalling, stabilise mitochondria, and inhibit inflammatory processes (Zhang and Li; Munjuluri et al. 2016 and 2021). Mechanistic studies demonstrate that Capsicum- or capsaicin-induced activation of TRPV1 initiates a cascade of prosurvival signalling, including the recruitment of anti-apoptotic kinases such as PI3K/Akt (phosphoinositide 3-kinase/protein kinase B). This activation reduces the production of reactive oxygen species (ROS) and suppresses pro-inflammatory cytokines, thereby collectively decreasing myocardial apoptosis during ischemia–reperfusion injury (Li et al., 2021). Piperine, the principal alkaloid of Piper species, exhibits comparable cardioprotective actions in vivo. Its beneficial effects are largely attributed to attenuation of oxidative stress, improvements in lipid profiles, and mitigation of post-infarct ventricular remodelling, mediated through antioxidant and anti-inflammatory pathways (Dulate et al., 2020). While there is some variability among studies with respect to differences in rodent species, dosing regimes and study quality, collectively, there is sufficient preclinical evidence to support the cardioprotective effects of capsicum/capsaicin and piperine as an explanation for the cardioprotective biochemical and physiological effects seen in experimental studies.

Table 4.1 — Some Selected preclinical studies (capsaicin/piperine)

Study (year)	Model	Intervention	Main findings
Zhang & Li (2016)	Rat/mouse I/R	Capsaicin pretreatment	↓ infarct size; TRPV1-CGRP-NO mediated vasodilation
Li et al. (2021)	Rodent I/R & cellular assays	Capsaicin/piperine	↑ PI3K/Akt signaling; ↓ NF-κB & ROS; improved survival
Dulate et al. (2020)	High-fat / cardiac remodeling models	Piperine supplementation	↓ oxidative stress; improved lipid profile; attenuated remodeling

Limitations: animal models use higher relative doses and controlled timing, not generalizable to typical human dietary exposures.

4.1.2 Population-level evidence

Epidemiological studies indicate that habitual consumption of chilli dishes is associated with long-term improvements in cardiovascular health. A recent systematic review of prospective cohort studies found an association between frequent chilli

consumption (14% – 18% lower relative risk of dying from CVD) compared to non or infrequent chilli consumers (Shi et al., 2021; Yamani et al.,2021). This association may be explained by past studies showing the biological effect of chilli in metabolising glucose, lipids and inflammatory substances as well as the favourable effect on endothelial cell function. There are, however, significant limitations on establishing a causal relationship between frequent chili consumption and reduced risk for CVD based on the size and geographic breadth of these cohort studies, the potential for residual confounding variables such as diet, socioeconomic status and physical activity and the differing methods used to measure chili exposure (i.e. frequency vs quantity of consumption and fresh vs processed chilies).

4.2 Adverse effects (clinical case reports)

Although population studies and preclinical studies suggest the possibility of long-term benefits, case reports have described acute ischemic events that occurred after exposure to either concentrated or non-food sources of pepper (Capsicum) at the same time. Case reports that show this include a patient who suffered a myocardial infarction after taking a concentrated capsaicin supplement (Capsaicin) (Baečić et al., 2012), a coronary vasospasm that happened at the same time as a capsaicin patch applied to the skin (Reilly et al., 2014), and some hypertensive or arrhythmia-type events that may have been caused by inhaling or using aerosolised pepper extract or oleoresin capsicum (Sogut et al., 2012). There are several possible explanations for these acute events, including overstimulation of TRPV1 causing increased neuropeptide release, increased heart rate and blood pressure due to sympathetic nervous system activation (causing increased oxygen demand on the heart) and coronary vasomotor instability due to abnormal vasorelaxation of the coronary arteries caused by either endothelial damage or abnormal smooth muscle reaction to some external stimulus. In all of these cases, the source of these acute events does not appear to be the consumption of pepper via the normal route (diet). In these reports, most of the acute events occurred after high-concentration or non-oral routes were used.

Table 4.2 — Representative clinical reports linking pepper exposures to ischemic events

Report (year)	Exposure	Clinical event	Mechanism proposed
Baečić et al. (2012)	Cayenne pill ingestion	ST-elevation MI	Sympathetic surge, coronary vasospasm
Reilly et al. (2014)	Topical capsaicin patch	Coronary vasospasm/angina	Systemic absorption → TRPV1 overstimulation
Sogut et al. (2012)	Pepper spray inhalation	Chest pain, hypertensive episodes	Airway nociceptor → sympathetic reflex

ATYPICAL CARDIAC PAIN: NEUROGENIC AND VASOSPASTIC EFFECTS

Atypical chest pain encompasses non-anginal chest sensations (burning, tightness) and pain syndromes with neurogenic or vasospastic mechanisms. Pepper-derived bioactives can contribute to such presentations through direct sensory activation, autonomic reflexes, and endothelial modulation.

5.1 Neurogenic chest pain

The ability of capsaicin to activate sensory C-fibres has been demonstrated through the elicitation of burning pain and hyperalgesia via the TRPV1 receptor. Activation of sensory fibres in the heart and oesophagus can give rise to a sensation of chest pain, which may be perceived as due to a cardiac aetiology in the absence of objective ischemia, and no other conditions exist that are known to induce chest pain in individuals without a cardiac aetiology. Furthermore, following the vigorous stimulation of nociceptors, there is a possibility of vagal-sympathetic interaction creating mixed autonomic dysfunctions (palpitations/lightheadedness) that may also complicate the clinical assessment of patients with mixed, thoracic, abdominal pain (Munjuluri et al., 2021). Inhalation of bronchoconstrictors and/or exposure to upper airway irritants such as pepper spray or occupational fumes may elicit discomfort in the chest that mimics symptoms associated with coronary artery supplies.

5.2 Coronary vasospasm

Concentrated amounts of capsaicin or particular terpenoids result in vasoconstriction due to a number of different physiological causes, including decreased endothelial NO response due to inflammation, increased intracellular calcium sensitivity of smooth muscle cells and increased sympathetic nervous system activity. Current literature includes case reports and small cohort studies that document acute coronary vasospasm following topical or concentrated exposure and therefore lend further support to the idea that volatile oils can induce vasospastic angina in patients who are predisposed to it (Reilly et al., 2014).

5.3 Inhalational exposure (pepper spray, occupational fumes)

The application of oleoresin capsicum (pepper spray) as well as other types of pepper-derived aerosols stimulates intense airway nociceptors, resulting in coughing, dyspnea, chest tightness, and sympathetic nervous system activation. Most people experience only mild respiratory and irritant symptomatology following an exposure; however, if someone was in an area with several people using pepper-based aerosol products or has been exposed frequently, they could experience the systemic effects of excessive sympathetic nervous system stimulation and low blood oxygen levels, which could lead to the development of ischemia in a susceptible person. In case series that followed these types of mass exposures, there was evidence of transient ECG changes, chest pain, and a rare case of ischemia; however definitive links can be difficult to demonstrate due to the number of confounding variables including the concomitant presence of stress at the moment of exposure, the presence of still being restrained, and already having preexisting cardiac disease (Sogut et al., 2012).

The aggregate evidence supports a bimodal model: habitual low-dose dietary exposure to pepper constituents is associated with

beneficial cardiometabolic and endothelial effects at the population level and in animal models, while acute, high-concentration, or non-dietary exposures carry a plausibly higher risk for triggering ischemic or neurogenic chest pain via sympathetic activation, vasomotor disturbances, or direct nociceptor activation. Clinicians should therefore obtain exposure histories (supplements, topical agents, pepper spray, occupational inhalation) when evaluating acute chest pain and consider objective cardiac testing rather than attributing symptoms solely to transient irritation.

RESEARCH GAPS IDENTIFIED

Although there have been numerous studies, including experimental, epidemiological, and clinical studies, much remains unknown about the cardiovascular effects of pepper-derived phytochemicals and volatile oils, thus leaving large knowledge gaps concerning the cardiovascular implications of these products. There is a lack of human-controlled clinical trials directly assessing how capsaicin or piperine affects coronary physiology. The majority of the data are derived from population-based studies or isolated case reports, therefore not establishing a cause-and-effect relationship for the hemodynamic effect of capsaicin or piperine ingestion (Zhang & Li, 2016; Munjuluri et al., 2021; Shi et al., 2021; Yamani et al., 2021), and the pharmacokinetic and pharmacodynamic profiles of inhaled or aerosolised volatile terpenoids (and some aerosolised capsaicinoids) remain poorly characterised for any rapid systemic absorption following inhalation or dermal exposure (Sogut et al., 2012). Consequently, despite data showing that concentrated extracts, patches and aerosols (oleoresin) can elicit sympathetic surges with possible vasospasm among susceptible individuals (Reilly et al., 2014; Baečić et al., 2012), there are no clinically established threshold doses that delineate safe doses from unsafe doses for concentrated extracts, patches or aerosols (oleoresin). Adverse events following pepper exposure and their association with cardiovascular disease are known to be underreported due to the lack of classification of pepper exposures as cardiac risk factors in most current surveillance systems. As a result, the current data on pepper-related cardiovascular adverse effects is limited, with the most common sources being sporadic case report sources and limited incidence data over longer time periods (Sogut et al., 2012; Baečić et al, 2012; Reilly et al, 2014). Additionally, our understanding of the mechanisms associated with these adverse effects is limited, with the majority of human studies missing critical data to identify the mechanisms relevant to human health and disease. The mechanisms are supported by multiple animal studies, which demonstrate involvement of TRPV1 overstimulation, depletion of CGRP, sensitisation of Ca^{2+} vasodependence of endothelin, and imbalances of nitric oxide (Munjuluri et al., 2021). Finally, the role neurogenic chest pain plays when triggered by the activation of C-fibres, airway irritation, or vagal versus sympathetic reflexes, remains both poorly understood and lacks a comprehensive approach to differentiate these presentations from ischemic chest pain in clinical practices (Munjuluri et al., 2021).

FUTURE RESEARCH DIRECTIONS

While currently available data show pepper-derived compounds have the ability to be both cardioprotective and cardiotoxic (depending on the type of exposure: acute or chronic), additional focused human research, better epidemiological surveillance systems, and improved mechanisms for understanding pepper-derived compound actions on the cardiovascular system need to be established to resolve these conflicting attributes. Priorities for furthering the understanding of this duality include conducting early phase randomised control trials to measure the immediate and long-term cardiovascular responses to dietary controlled exposures of capsaicin and piperine (focusing on their effects on coronary flow reserve, endothelial function, autonomic tone, and ischaemic thresholds) in both healthy participants and those with a diagnosis of stable coronary artery disease (Zhang & Li, 2016; Qin et al., 2017; Munjuluri et al., 2021). Likewise, more comprehensive pharmacokinetic and pharmacodynamic research using the oral, topically applied, and inhalational forms of pepper-derived compounds will be needed to create a complete picture of their systemic absorption, metabolic processes, and distribution to tissues; thus allowing for the correlation of clinical and preclinical evidence with markers of capsaicin and piperine's effects such as calcitonin gene related peptide release and nitric oxide metabolite concentrations. Additionally, the correlation of diseases produced by excessive exposures will enable a complete understanding of the potential side effects associated with abnormal use of pepper products; thus, furthering the development of safe limits of exposure (Sogut et al., 2012; Çil, 2012; Tripathi et al., 2022). Furthermore, developing a system to accurately document the temporal relationship of cardiovascular events associated with pepper products through the implementation of multi-centre registries aligned with the pharmacovigilance systems of the FDA and the EMA will allow for better estimates of the incidence and identification of risk factors for these events (Gliklich et al., 2014; FDA, 2018; Vasilakes et al., 2019). Recent technological advances regarding TRPV1 PET tracers for in vivo Molecular Imaging and new stress perfusion-type MRI for Cardiac Patients provide more opportunities to see how human Receptor Expression / Activation in the Heart are affected by several physiological factors (Hurt et al., 2016; Tateishi et al., 2024). However, by integrating Imaging-PD/PK Data through Mechanistic Models and Monte Carlo Simulations, we may be able to establish a Safe Therapeutic Window for the use of Pepper-based complements in Topical Application (Tripathi et al., 2022; Vasilakes et al., 2019).

There is an urgent need to evaluate the Synergistic / Antagonistic Interactions between Key Terpenoids (e.g., beta-caryophyllene, limonene, linalool) on TRPV1 Signalling, Vascular Tone, and Capsaicin Desensitisation through in-vitro, in-vivo, and Microdosing Studies (Gertsch et al., 2008; Salehi et al., 2019). In addition, further research should focus on Drug Nutrient Interactions (e.g., Piperine's Influence on CYP and UGT Pathways) and Investigation of Populations at Risk (e.g., CAD, Vasospastic Angina, elderly patients, and Pregnant Women) (Tripathi et al., 2022).

CONCLUSION

Phytochemicals derived from peppers and chillies, including capsaicinoids, piperine, and associated volatile terpenoids, exhibit a broad spectrum of biological effects that extend well beyond their culinary applications. Evidence from in vitro experiments, animal models, clinical observations, and epidemiological studies collectively supports the view that low-level dietary exposure to these compounds is associated with cardioprotective effects. These benefits appear to be mediated through convergent mechanisms, including TRPV1-dependent vasodilation, nitric oxide–driven improvement of endothelial function, attenuation of oxidative stress, and suppression of inflammatory signalling. Epidemiological data further reinforce these mechanistic findings

by demonstrating inverse associations between habitual chilli consumption and cardiovascular mortality.

In contrast, the cardiovascular effects of pepper-derived compounds are strongly influenced by dose and route of exposure. Concentrated formulations and non-dietary routes, such as inhalational or transdermal exposure, may produce excessive TRPV1 activation, sympathetic stimulation, and transient elevations in heart rate and blood pressure, thereby increasing the risk of coronary instability, vasospasm, and, in rare cases, ischemic injury. Importantly, chest discomfort following pepper exposure may arise not only from myocardial ischemia but also from neurogenic, vasospastic, or musculoskeletal mechanisms, complicating clinical assessment and increasing the potential for misdiagnosis, particularly in occupational and emergency medicine settings.

Despite the expanding use of pepper-derived supplements and topical products, substantial gaps remain in the human evidence base. There is a lack of controlled clinical studies examining coronary physiology, autonomic responses, dose–response relationships, and pharmacokinetic–pharmacodynamic profiles across exposure routes. In addition, potential interactions among capsaicinoids and terpenoids remain poorly characterised, and cardiovascular adverse events may be underreported due to limited surveillance and diagnostic awareness.

Overall, these findings underscore the dual nature of pepper-derived phytochemicals, highlighting both cardiometabolic benefit at dietary levels and cardiovascular risk at concentrated exposures. Future research should prioritise mechanistically informed, exposure-specific human studies, enhanced adverse event monitoring, and improved risk stratification to define safe therapeutic windows and identify vulnerable populations. Such efforts are essential to support the evidence-based translation of pepper-derived compounds from dietary components to potential cardiovascular interventions.

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