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# Resveratrol and derivatives for the treatment of atrial fibrillation

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**Resveratrol is a bioactive polyphenol, found in grapes, red wine, and peanuts, and has recently garnered much media and scientific attention for its diverse beneficial health effects as a nutritional supplement or nutraceutical. Of particular interest are the well-documented cardioprotective effects of resveratrol that are mediated by diverse mechanisms, including its antioxidant and vascular effects. However, it is now becoming clear that resveratrol may also exhibit direct effects on cardiac function and rhythm through modulation of signaling pathways that regulate cardiac remodeling and ion channel activity that controls cardiac excitability. Resveratrol may therefore possess antiarrhythmic properties that contribute to the cardiovascular benefits of resveratrol. Atrial fibrillation (AF) is the most common cardiac arrhythmia, although current therapies are suboptimal. Our laboratory has been studying resveratrol's effects on cardiac ion channels and remodeling pathways, and we initiated a drug development program aimed at generating novel resveratrol derivatives with improved efficacy against AF when compared to currently available therapeutics. This review therefore focuses on the effects of resveratrol and new derivatives on a variety of cardiac ion channels and molecular pathways that contribute to the development and maintenance of atrial fibrillation.**

**Keywords:** atrial fibrillation; resveratrol; ion channels; drug design; arrhythmias

## Atrial fibrillation: a major health concern with suboptimal treatment

Atrial fibrillation (AF) is the most common type of cardiac electrical rhythm disturbance, and the incidence of AF is increasing in most developed countries as a result of the aging population.[1–4] While AF does not generally induce sudden cardiac death, AF is the primary cause of 15% of strokes[5,6] and can also cause adverse remodeling of the heart leading to heart failure (HF).[1,5,7,8] Furthermore, 30–40% of patients undergoing coronary artery bypass graft (CABG) surgery develop transient postoperative AF that may develop into permanent AF.[9] While direct current cardioversion (DCC) remains the standard of care for AF, there are associated risks and costs associated with this procedure, DCC is not always successful,[10] and not all centers can perform DCC within an adequate time frame.

In addition, the prevalence of AF increases with age, with 0.5% of patients affected in the 50-year-old range and ~10% over the age of 80,[11] and the prediction is that it will increase in the future.[12] HF and AF are often diagnosed in the same patient, and those with HF are more likely to develop AF compared to the general population.[13] The presence of AF in HF patients with either preserved or reduced left ventricular function carries an increased risk for all-cause mortality.[14] In patients with HF or AF, the development of the other condition leads to further deterioration of an already poor prognosis. The analysis of the relationship of AF and HF in patients from the Framingham Heart Study revealed that, in patients with HF, later development of AF was associated with increased mortality in both sexes.[13] As such, AF and HF were called the "two new epidemics of cardiovascular disease."[15] Many underlying diseases are common risk factors for both HF and

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AF, including hypertension, valvular heart disease, coronary artery disease, and diabetes.[16] These conditions, either collectively or individually, may eventually lead to structural and electrophysiological remodeling[17] and sustained neurohormonal activation that promote the development of AF and HF.[18] Once established, AF can promote HF owing to rapid ventricular rate, leading to tachycardia-induced cardiomyopathy and associated myocardial maladaptive remodeling.[19] Therefore, early therapeutic interventions to reduce AF may also reduce the burden of the more serious disease of HF.

However, despite the increasing burden of AF and its association with HF, current pharmacotherapy for the prevention and treatment of AF still has major limitations,[3,4] and relies on either (1) rate control with β-blockers, glycosides, and calcium channel antagonists,[20,21] or (2) rhythm control[2,21] using either class I antiarrhythmics, such as propafenone and fleciainide, or class III antiarrhythmics, such as amiodarone, dronedarone, and dofetilide. The multichannel inhibitor amiodarone is the most effective, orally bioavailable drug; however, its use is limited by its very long half-life, negative drug–drug interactions, severe extracardiac side effects, and significant risk for acquired long-QT (LQT) syndrome and *torsade de pointes* arrhythmias.[22,23] Dronedarone, an analogue of amiodarone, was designed to have an improved pharmacokinetic and safety profile; however, the recent PALLAS trial evaluating dronedarone in patients with permanent AF (>7 days) was stopped prematurely owing to a lack of efficacy in converting permanent AF and increasing heart failure events.[24] In addition, dronedarone was found to increase mortality in patients with significantly reduced left ventricular function in HF in the ANDROMEDA trial.[25]

Vernakalant (Brinavess™), a multi-ion channel blocker developed by Cardiome Pharma Corp., is currently the only atrial-selective antiarrhythmic drug approved for IV use in Europe,[26,27] although it has not been approved in North America. Although only ∼50% of patients are responsive to vernakalant,[28] it is nevertheless the best-in-class AF IV therapeutic currently available for the management of acute AF. Until recently, an oral formulation of vernakalant was being developed in partnership with Merck; however, further development was discontinued in March 2012. It was reported that this decision was based upon "Merck's assessment of the regulatory environment and projected development timeline." As such, there is still a large unmet need for the development of improved oral antiarrhythmic compounds for AF[29] that are also atrial specific and exhibit few side effects.[30]

## Cellular etiology of AF and potential drug targets

In an attempt to maintain proper cardiac function and intracellular homeostasis in response to pathophysiological processes involved in cardiovascular diseases, including HF and AF development, a number of electrophysiological and structural changes occur in the heart, collectively described as myocardial remodeling.[1,17,31] These alterations are partly adaptive in nature; however, when maintained for longer periods they can lead to further deterioration of cardiac function resulting in HF, and can also significantly contribute to the development and maintenance of ventricular and atrial arrhythmias such as AF. Over the last decade, the cellular mechanisms underlying AF have been extensively investigated and include alterations in ion channel expression and chronic activation of signaling pathways controlling cellular remodeling.

Improved knowledge of the mechanisms underlying AF represents a key opportunity to develop novel atrial-specific therapies for the treatment of AF, and, in this regard, several promising therapeutic targets have been revealed for potential drug development. One important atrial-specific target is the Kv1.5 ($I_{Kur}$), a potassium channel expressed in the atria, but not the ventricles.[32] In addition to Kv1.5, late sodium current (late $I_{Na}$),[33] overactive $I_{KACh}$ channels,[32,34,35] inflammation/oxidative stress,[36] and activation of the nuclear factor of activated T cells (NFAT)[37] have all been implicated in the development of AF.

Therefore, on the basis of the available information, an ideal multifunctional small molecule drug for AF should possess the following properties: (1) frequency-dependent Kv1.5 inhibition, (2) late $I_{Na}$ inhibition, (3) $I_{KACh}$ channel inhibition, (4) lack of hERG channel inhibition to reduce the likelihood of drug-induced LQT syndrome,[38] (5) atrial specificity, (6) antioxidant properties, and (7) NFAT inhibition. The complex etiology of AF and the multiple mechanisms responsible for the development and maintenance of AF led to the suggestion that novel

compounds targeting several pathways involved in AF may exhibit improved efficacy.[29,39]

## Resveratrol: a parent molecule for AF drug design?

Since reports of the "French paradox" came to light,[40–42] suggesting red wine consumption as beneficial to cardiovascular health, there have been numerous studies on the polyphenolic constituents of red grape products.[43,44] It is now clear that resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is one of several bioactive polyphenols that may be potentially harnessed for the treatment of many diseases including cardiovascular disease.[43,45,46] In addition, when given orally, resveratrol is remarkably well tolerated and exhibits very few side effects, which collectively contribute to its popularity as a nutritional supplement.[47] However, more human data are required from well-executed clinical trials, as much of the evidence fueling resveratrol's fame comes from preclinical data from rodents.[45,46,48] Translation of the effects of resveratrol observed in preclinical animal studies into humans therefore remains a challenge.[49,50]

Through intense research efforts, resveratrol has been shown to exhibit pharmacological activity against many diverse cellular signaling pathways in a wide range of tissues that are involved in diseases that include cancer, aging-related degenerative diseases, inflammation, cardiovascular disease, obesity, and diabetes.[46,51] With respect to the direct effects of resveratrol on the heart, previous studies have already demonstrated the beneficial effects of resveratrol against HF[52] and ventricular arrhythmias in the setting of ischemia/reperfusion injury[53] in rodents. Moreover, a recent study has shown that resveratrol reduces AF susceptibility in the failing heart via the PI3K/Akt/eNOS signaling pathway.[54]

With respect to remodeling in AF, the rapidly contracting atria may lead to imbalances in calcium homeostasis and subsequent calcium loading that lead to chronic activation of the calcium-sensitive phosphatase calcineurin.[37,55,56] NFAT dephosphorylation by calineurin allows its activation and translocation into the nucleus to activate a pro-hypertrophic gene transcription program in the heart.[57–59] Such transcriptional activity likely contributes to marked alterations in the gene profiles of atria from patients with AF.[60] Notably, resveratrol has been shown to inhibit this hypertrophic cardiac remodeling process via activation of AMP-activated kinase (AMPK) and subsequent inhibition of NFAT activation,[61,62] which has been implicated in the development of AF,[37] pathological cardiac hypertrophy, and HF.[52,57]

In addition to resveratrol's ability to beneficially alter cardiac structural and electrical remodeling in the setting of hypertrophy, HF, and AF, this polyphenol also exerts a direct effect on several cardiac ion channels that are responsible for the maintenance and propagation of the cardiac action potential that forms the basis of appropriate electrical activity and correct excitation–contraction coupling. In particular, inhibition of late $I_{Na}$ has emerged as a potential therapeutic strategy for the treatment of ischemia/reperfusion injury,[63] HF, and AF.[33] In this regard, several studies have indicated that inhibitory effects of resveratrol and derivatives on voltage-gated sodium channels contributed to their antiarrhythmic actions. With respect to late $I_{Na}$, resveratrol inhibited $H_2O_2$-induced augmentation of late $I_{Na}$ in rat ventricular myocytes[9] and inhibited oxidative stress–induced arrhythmogenic activity in rabbit ventricular myocytes through inhibition of late $I_{Na}$. However, these studies did not separate the antioxidant effects of resveratrol from any direct effects on late $I_{Na}$. In this respect, our group previously published a comprehensive study of the direct effects of several polyphenols on human voltage-gated sodium currents.[64] In contrast to lidocaine, resveratrol did not exhibit any frequency dependence of the peak $I_{Na}$ block, although late $I_{Na}$, induced by the long-QT mutant R1623Q or the sea anemone toxin ATX II, was reduced by resveratrol. In field-stimulated ventricular myocytes, ATXII-induced increases in diastolic calcium concentration and contractile dysfunction were prevented and reversed by resveratrol.[64] These data support the concept that resveratrol has a direct inhibitory effect on late $I_{Na}$ that results in reduced electrical and contractile dysfunction. Collectively, these studies indicate that resveratrol inhibits several pathways involved in the development of AF, although we found that resveratrol is a poor inhibitor of the atrial-specific Kv1.5 potassium channel ($IC_{50} = 66\ \mu M$) that is a major potential therapeutic target for AF.[32]

On the basis of this evidence of the potential for multifunctional biological activity of resveratrol in HF and AF, we speculated that nature may already

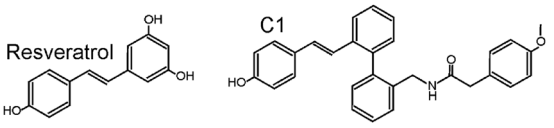


**Figure 1.** Chemical structures of resveratrol and compound 1 (C1).

have provided an ideal starting template for rational drug design of novel AF therapeutics. Therefore, our group initiated a drug development program, using resveratrol as the parent compound, in an attempt to optimize its Kv1.5 and $I_{KACh}$ inhibitory profile while maintaining antioxidant and NFAT/late $I_{Na}$ inhibitory efficacy. Accordingly, we synthesized several compounds by combining resveratrol with a known Kv1.5 inhibitor AVE0118 and identified a novel compound (compound 1, C1, (Fig. 1)). C1 dose-dependently inhibited peak and late Kv1.5 ($IC_{50}$ = 0.36 and 0.11 μM, respectively), $I_{KACh}$ ($IC_{50}$ = 1.9 μM), peak $I_{Na}$, and late $I_{Na}$ ($IC_{50}$ = 3.0 and 1 μM, respectively). C1 also displayed marked frequency-dependent Kv1.5 inhibition and was a much more potent inhibitor at stimulation rates of 3 Hz compared to 1 Hz.[65] Collectively, such an ionic pharmacological profile may serve to prevent either adverse action potential shortening through increased Kv1.5 or $I_{KACh}$ activity or excessive action prolongation through induction of late $I_{Na}$, resulting in maintenance of the action potential duration (APD) in an optimal range to reduce the occurrence of AF (Fig. 2).

With respect to nonionic effects, C1 also demonstrated NFAT-inhibitory and antioxidant properties that were similar to those of the parent molecule resveratrol.[65] This effect is likely owing to activation of AMPK that suppresses NFAT activation and is a known target of the parent molecule resveratrol, although the effects of C1 on AMPK remain to be tested experimentally. Although the effects of C1 on structural remodeling and fibrosis remain to be tested experimentally, resveratrol has been shown to markedly reduce cardiac fibrosis in a rat model of pressure-overload hypertrophy.[66] It has also been demonstrated that resveratrol may impart some of its cardioprotective effects through inhibition of the renin–angiotensin system,[67] and this possibility remains to be explored with respect to resveratrol and C1 in the setting of AF.

With reference to nonatrial effects, C1 displayed no effects on calcium handling or contractility in isolated ventricular myocytes, suggesting that, at concentrations effective at modulating atrial ion channels, C1 will have little effect on ventricular excitation–contracting coupling in ventricular tissue, although any effects on calcium handling in atrial tissue remain to be determined. These results indicated that C1 may possess beneficial and atrial-specific antiarrhythmic properties for AF. To test this notion, we used an atrial tachypacing–induced canine AF model and found that C1 was effective at reducing the onset and duration of AF episodes at a dose of 1 mg/kg (I.V. bolus), which resulted in a blood plasma concentration of ∼1 μM.[65]

Importantly, C1 showed only weak hERG channel inhibition ($IC_{50}$ = 30 μM), displaying ∼100-fold selectivity for Kv1.5 inhibition over hERG. Moreover, C1 did not prolong the QT interval in conscious dogs, suggesting that the compound did not significantly influence ventricular repolarization and was unlikely to provoke long QT–induced and *torsade de pointes* ventricular arrhythmias at the concentrations tested in these experiments. A conclusion, based on these effects, is that C1 holds promise as a multifunctional small molecule by

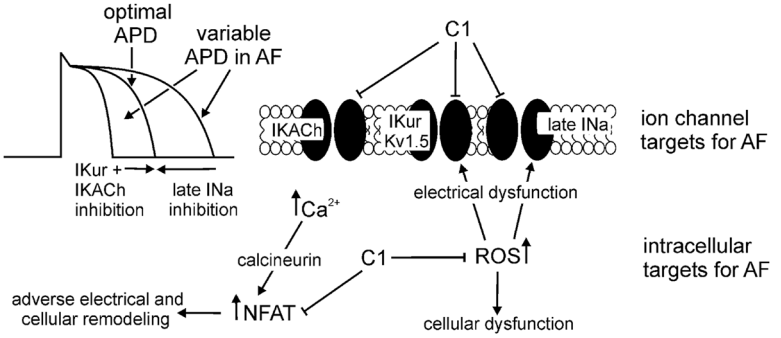


**Figure 2.** Proposed cellular mechanisms of action for the anti-AF effects of resveratrol derivatives such as C1.

targeting several key pathways known to be involved in the development and maintenance of AF (Fig. 2).

## Future directions

There are several major hurdles to overcome in the design of orally available small molecules for long-term prophylactic therapy, such as achieving adequate absorption and resistance to metabolic degradation/modification, that collectively contribute to prolonged circulating plasma levels of an effective dose of the biologically active drug. However, as a parent molecule, resveratrol is not an ideal starting compound in these respects. For example, although resveratrol is well absorbed through the gut wall, it is rapidly metabolized into by-products and metabolites or cleared in the urine.[68–70] Therefore, the effective concentrations and half-life of unmodified resveratrol in the plasma are very low, with the half-life being measured at 49 min in healthy volunteers.[69,71] As such, the pharmacokinetic profile of resveratrol is not ideally suited to pharmacological development, although this may be enhanced significantly through formulation.[71] Nevertheless, resveratrol itself is a naturally occurring polyphenol with few side effects that shows great promise as a parent molecule for the design of much needed novel drugs for the treatment of AF, and efforts are underway in our laboratory to strike the delicate balance between improving the biological activity of resveratrol derivatives with respect to multiple AF targets while improving upon the suboptimal pharmacokinetics observed in the parent resveratrol molecule. In the meantime, human trials on the effects of resveratrol for the prevention of AF should be pursued, especially in the more controlled acute setting of elective cardiac surgery such as CABG, where postoperative AF occurs in 30–40% of patients.[9]

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## Conflicts of interest

The authors declare no conflicts of interest.

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