Title

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Journal

The Annual Review of Pharmacology and Toxicology, 62(1)

ISSN

0362-1642

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Publication Date

2022-01-06

DOI

10.1146/annurev-pharmtox-052120-104249

Published in final edited form as:

Annu Rev Pharmacol Toxicol. 2022 January 06; 62: 447–464. doi:10.1146/annurev-pharmtox-052120-104249.

KCNQ Potassium Channels as Targets of Botanical Folk Medicines

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Abstract

Since prehistory, human species have depended on plants for both food and medicine. Even in countries with ready access to modern medicines, alternative treatments are still highly regarded and commonly used. Unlike modern pharmaceuticals, many botanical medicines are in widespread use despite a lack of safety and efficacy data derived from controlled clinical trials and often unclear mechanisms of action. Contributing to this are the complex and undefined composition and likely multifactorial mechanisms of action and multiple targets of many botanical medicines. Here, we review the newfound importance of the ubiquitous KCNQ subfamily of voltage-gated potassium channels as targets for botanical medicines, including basil, capers, cilantro, lavender, fennel, chamomile, ginger, and *Camellia*, *Sophora*, and *Mallotus* species. We discuss the implications for the traditional use of these plants for disorders such as seizures, hypertension, and diabetes and the molecular mechanisms of plant secondary metabolite effects on KCNQ channels.

Keywords

anticonvulsant; epilepsy; herbal medicine; hypertension; M-current; voltage gated

INTRODUCTION

Diets rich in fruits, vegetables, and herbs are often strongly encouraged as these plants tend to offer tremendous health benefits and decreased risks for a variety of diseases (1-3). This is in no small part due to their production of bioactive molecules that are capable of beneficial interactions with specific protein targets, most of which remain to be elucidated. Many of these bioactive molecules are flavonoids—water-soluble, polyphenolic compounds—but they can also be other plant secondary metabolites, such as fatty aldehydes (4-6).

These plant metabolites not only are important for long-term health purposes, as part of a healthy and balanced plant-rich diet, but also could contribute to why some plants have

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DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

been used for medicinal treatments for specific disorders. The rich history of the use of therapeutic plants by hominid species may date as far back as 800,000 years, when *Homo erectus* or similar species consumed herbs that are used as folk medicines today (7). There is also evidence that *Homo neanderthalensis* consumed chamomile and willow bark—bitter plants, offering little nutritional value—likely for therapeutic purposes (8, 9). Particularly compelling is the finding that of several *Homo neanderthalensis* skulls for which the dental calculus was analyzed, DNA from willow bark was discovered only in the skull that also contained a tooth abscess. This finding suggests that Neanderthals used willow bark as a painkiller (9). The molecular basis for this is partly explained by salicin, a chemical in willow bark that is structurally similar to aspirin (acetylsalicyclic acid). Aspirin is an irreversible inactivator of the cyclooxygenase (COX) enzyme that is needed for prostaglandin and thromboxane synthesis, explaining its dual effects in blocking pain transmission (mediated by prostaglandins) and blood clotting (mediated by thromboxanes). Willow bark contains insufficient salicin levels to produce the COX inhibition produced by a typical aspirin dose; instead, it is a combination of salicin and other flavonoids and polyphenols in willow bark that produces a broad-spectrum anti-inflammatory and analgesic effect, which incidentally lacks the blood clotting inhibition caused by aspirin (10). Thus, willow bark can be superior to aspirin and can be used by some patients for which aspirin is contraindicated (10). This encapsulates the paradox of the desire we have in the modern era to investigate traditional medicines, discover the active component, and utilize it in pure form; in many cases, the whole-plant extract was in traditional use because of the safety and efficacy of the mixture, which can be lost when purifying and using individual components.

As the human species evolved and civilizations formed, most relied upon plant and herb-based remedies to treat ailments. The ancient Egyptians (ca. 4000–1000 BCE) are credited with developing one of the earliest writing systems, and some of their records describe elaborate and effective pharmacological treatments using natural resources (11, 12). Indeed, as is suspected for the Neanderthals long before them, the Ancient Egyptians used willow bark as an analgesic, perhaps applying principles passed down to them from earlier, less complex societies by word of mouth or by observation. Hippocrates also described the use of willow bark as an analgesic, particularly for pain during childbirth (13). In the late 1700s, the efficacy of willow bark in treating fever was demonstrated for the first time using a rigorous controlled scientific approach. In 1831, salicin was discovered and found to be a biomarker for the therapeutic activity of willow bark. Shortly after, in 1853, sodium salicylate was treated for the first time with acetyl chloride to generate aspirin. In 1971, John Vane discovered the molecular therapeutic targets of aspirin, for which he won the Nobel Prize in Physiology or Medicine in 1982, completing the long road from the medicinal usage of willow bark as many as 50,000 years ago to the relatively recent discovery of its mechanisms of action (14, 15).

In the early 1800s, Friedrich Sertürner founded alkaloid research by extracting morphine from opium—making him the first person to isolate the active component from a medicinal plant (16). Then, in the 1930s, chemists began to synthesize pharmaceuticals that could be more potent than the natural products, though the structure of synthetic compounds often resembles those found in nature. Even so, 11% of the 252 drugs that the World Health Organization considers basic and essential originated exclusively from flowering plants (17).

Additionally, as many as 80% of the population in the developing world still relies on natural products for medicine (17), and many in developed countries still regard them as alternative treatments. For example, in 1997, an estimated 42.1% of US adults (83 million) used alternative therapies (18).

Despite how common the use of these treatments is, many do not have well-characterized mechanisms of action or identified bioactive components. Additionally, there are many plants that have not yet been studied or analyzed that could lead to the identification of more medicinal plants/compounds—for example, 98.6% of plants in Brazil, the most biodiverse country in the world, have not been studied chemically according to one estimate (19). To find ways to efficiently utilize these plants and compounds, we need to efficiently screen them, which is expedited by having potential drug targets to screen against. In this review, we focus on the use of the KCNQ subfamily of voltage-gated potassium (Kv) channels as a drug target to screen for plants with known or potential medicinal properties and discuss recent studies identifying plants and compounds capable of activating these channels.

KCNQ CHANNELS AS DRUG TARGETS

KCNQ channels constitute a subfamily of Kv channels and are found in both excitable and nonexcitable cells (20). There are five genes (*KCNQ1–5*) that each encode pore-forming α subunits containing six transmembrane domains. S1–S4 compose the voltage-sensing domain (VSD), and S5–S6 form the pore module (21) (Figure 1a). These gene products can homo- or heterotetramerize with other KCNQ α subunits to form an active channel. Since these channels are voltage gated, they respond to cellular membrane depolarization, which causes the VSD to move and the pore to open—allowing for outward potassium diffusion (20) (Figure 1b). This outward K^+ flux repolarizes excitable cells, regulates action potential frequency and morphology, and regulates processes in nonexcitable cells that include movement of other ions and solutes, fluid homeostasis, and hormone production and secretion. KCNQ channels are expressed throughout the body and play key roles in many physiological processes (21).

KCNQ2/3, KCNQ3/5, and potentially KCNQ2, KCNQ3, and KCNQ5 homomers form channels that generate the muscarinic-inhibited M-current, a subthreshold Kv current that regulates neuronal firing. Though KCNQ channels are characterized as voltage gated because they open in response to membrane depolarization, they have also been shown to respond to endogenous and exogenous small molecules and, indeed, require binding of the soluble lipid-derived signaling molecule phosphatidylinositol 4,5-bisphosphate for activity (22-24). A variety of small molecules can interact with KCNQ channels to shift their voltage dependence of activation to more hyperpolarized potentials, causing them to activate at more negative membrane potentials. This response to small molecules, in addition to their important physiological roles, makes these channels a potential drug target for a variety of diseases.

KCNQ2/3 channels are prominently expressed at the axon initial segment and at nodes of Ranvier; at these locations, neuronal KCNQ channels can act as gatekeepers to regulate neuronal firing and nervous transmission. Accordingly, dysfunction in neuronal KCNQ

channels can lead to severe epileptic encephalopathies (20, 25, 26). Because of this, efforts were made to find small molecules that can augment KCNQ2/3 currents, especially at subthreshold voltages, where increased KCNQ channel activity can help prevent aberrant or excessive neuronal firing. Out of these efforts emerged retigabine (ezogabine), a small molecule that binds in a pocket between the S5 and VSD of neuronal KCNQ channels. Especially important is a tryptophan on the S5 segment (W265 in human KCNQ3), which is present in KCNQ2–5 but lacking in KCNQ1, explaining the insensitivity of the latter to retigabine and derivatives such as ML-213 (27, 28). When interacting with W265 by hydrogen bonding, utilizing its carbonyl oxygen as an H-bond acceptor (27), retigabine is able to negative-shift the voltage dependence of KCNQ2–5 activation, opening the channels at more negative membrane potentials than normal and thus greatly increasing current at the subthreshold potentials, raising the barrier for neuronal firing and providing antiepileptic effects (29, 30). Unfortunately, despite clinical efficacy, retigabine was removed from clinical use in June 2017 due to side effects, including skin discoloration and urinary retention because of effects on bladder smooth muscle (31).

Subsequent studies from the authors' lab (32, 33) identified that the retigabine binding site evolved to accommodate endogenous ligands, including the inhibitory neurotransmitter γ-aminobutyric acid (GABA), which, like retigabine, is thought to rely on a carbonyl group to interact with KCNQ3-W265 and KCNQ5-W270 and thus augment channel activity by hyper-polarizing the voltage dependence of activation. The binding pocket is lined by KCNQ3-W265 on the S5 and KCNQ3-R242 at the foot of the voltage sensor (and their equivalents in other KCNQ isoforms) (Figure 1c), a channel location highly influential in gating processes, consistent with the effects of small molecules that can bind there.

Interestingly, GABA binds to KCNQ2–5 but only activates isoforms KCNQ3 and KCNQ5, unlike retigabine. Other compounds with similar chemical properties (specifically, a negative electrostatic surface potential centered around a carbonyl group) and activity to GABA, and a similar binding site in neuronal KCNQ channels, include the lesser-known neurotransmitter and weak anticonvulsant γ-amino-β-hydroxybutyric acid (GABOB), which acts as a high-potency partial agonist for KCNQ3, and the ketone body β-hydroxy-butyric acid (BHB), which activates both KCNQ3 and KCNQ5 with similar efficacy and potency to that of GABA (33). BHB activation of neuronal KCNQ channels may contribute to the anticonvulsant effect of the ketogenic diet (34). In addition, the synthetic GABA analog gabapentin, but not the related gabapentinoid pregabalin, binds to and activates KCNQ3 and KCNQ5 via the retigabine/GABA binding pocket with high potency (35). As discussed below, some plant secondary metabolites also occupy this pocket to produce their therapeutic effects.

KCNQ1, KCNQ4, and KCNQ5 are expressed in vascular smooth muscle and regulate vascular tone (36-38). KCNQ5 has been suggested as a drug target for blood pressure–lowering medications. KCNQ4 is also expressed in auditory neurons and hair cells, where it is necessary for hearing (39). KCNQ1 channels utilize ancillary peptides (KCNE1–5), allowing them to play a variety of roles in both excitable and nonexcitable cells. For example, KCNQ1/KCNE1 produces the slow-activating cardiac delayed rectifier K^+ current, I_{Ks}, which is expressed in ventricular cardiomyocytes, where it is important for ventricular

repolarization. Thus, mutations in KCNQ1 and KCNE1 can cause the electrocardiogram abnormality Long QT syndrome (21).

MALLOTUS OPPOSITIFOLIUS ANTICONVULSANT ACTION EXPLAINED BY KCNQ INTERACTION

The African shrub *Mallotus oppositifolius* (Figure 2a) has traditionally been used to treat a variety of ailments, as have other species from the *Mallotus* genus, across Africa and Asia (40). *M. oppositifolius* leaves are used for treating parasites, eye and kidney infections, pain, paralysis, headaches, swelling, and spasms. Its roots have been used to treat anemia and pneumonia, as well as being used as an aphrodisiac (41). There has also been much interest in the use of *M. oppositifolius* as an anticonvulsant. In a pentylenetetrazole (PTZ) chemoconvulsant seizure assay, it was found that *M. oppositifolius* leaf extract both delayed the onset and reduced the duration of PTZ-induced clonic and tonic seizures in mice (42).

Subsequent mechanistic studies uncovered that the anticonvulsant action of *M. oppositifolius* is partly due to one of its constituent polyphenols, mallotoxin (MTX; also known as rottlerin) (Figure 2b), which was previously identified by mass spectrometry as being present in *M. oppositifolius* as well as in other *Mallotus* species used in folk medicine, including *Mallotus philippensis*. Though Matschke et al. (43) found that MTX activates KCNQ1 and KCNQ4 but not KCNQ2, KCNQ5, or KCNQ2/3, this was likely due to screening for activation at +40 mV, which can fail to identify compounds that activate through shifting the voltage dependence of activation. By observing the effects at more hyperpolarized potentials, such as −80 mV and −60 mV, it is easier to distinguish the change in voltage dependence, as was seen by Manville & Abbott (44). Using this approach, we see that at −60 mV, 100 μM MTX increases the KCNQ2/3 current sevenfold, with an EC_{50} of 11.5 ± 0.2 μM (Figure 2c). Despite this action on KCNQ2/3 channels, MTX is relatively ineffective at protecting mice from PTZ-induced seizures (44).

The missing component was found to be isovaleric acid (IVA) (Figure 2b), another chemical that is present in *M. oppositifolius* leaf and also in valerian root, a folk medicine that has been used since ancient Greece to treat anxiety and insomnia and was used between at least the sixteenth and nineteenth centuries as an anticonvulsant (45, 46). IVA, which structurally resembles GABA, was found to also activate KCNQ2/3 channels, with a shift in $V_{0.5activation}$ of −11 mV. Together, MTX and IVA synergize to produce a 24-fold increase in current at −60 mV (Figure 2d), with a $V_{0.5activation}$ shift of −23 mV.In a PTZ chemoconvulsant assay, MTX (20 mg/kg) halved the colonic seizure incidence, although IVA (20 mg/kg) had no effect. However, the combination of MTX and IVA (10 mg/kg each) also halved the clonic seizure incidence, while neither MTX nor IVA reduced seizures at 10 mg/kg on their own, demonstrating that the anticonvulsant properties of *M. oppositifolius* are due to the synergistic activation of KCNQ2/3 channels by MTX and IVA (44).

The molecular basis of this synergy was resolved by in silico docking simulations and comparison of isoform selectivity and the effects of binding site mutagenesis using in vitro electrophysiology. IVA's activity depended on the S5 Trp residue also required by GABA and retigabine (Figure 2e). MTX, the structure of which is less similar to that of GABA

(and lacks the negative electrostatic surface potential localized to the carbonyl group on GABA, retigabine, and IVA), docked closer to an arginine residue located at the foot of the voltage sensor (Figure 2f) and indeed required the arginine for its action (47); MTX was relatively less dependent on the S5 Trp (44). Docking and mutagenesis studies both pointed to MTX and IVA binding in different locations in a similar binding pocket (Figure 2g) to synergistically activate KCNQ2/3 channels (44).

Interestingly, retigabine synergized further with IVA and MTX to lock open the KCNQ2/3 channel, with docking studies and the different isoform preferences of the compounds (IVA and MTX prefer KCNQ2, retigabine prefers KCNQ3) supporting a model in which the three compounds leveraged the heteromeric composition of KCNQ2/3 channels to synergistically activate them. The triple combination also enabled much lower doses of retigabine than normal to effectively activate KCNQ2/3, suggesting an approach in which addition of the three chemicals in combination could be used to overcome the side effects of retigabine that resulted in it being removed from clinical use (44).

M. oppositifolius also has reported antidepressant effects. Interestingly, Friedman et al. (48) identified KCNQ channels as being a potential drug target for depression. They found that increasing KCNQ3 expression induced an antidepressant effect in a mouse model of depression. Although MTX and IVA are more active upon KCNQ2 and KCNQ2/3 than on KCNQ3, the authors did not overexpress KCNQ2, so it is possible this interaction could also be responsible for the reported antidepressant effects.

KCNQs, CILANTRO, AND FITWEED

Archaeological evidence in Israel of the use of cilantro (*Coriandrum sativum*) (also known as coriander) dates back at least 8,000 years. Cilantro is also thought to have been cultivated by the Egyptians, as it was found in the tomb of Tutankhamen (49). Though cilantro is now mainly known for its uses in the kitchen as a culinary herb, garnish, and flavoring for a range of foods, it also has reported therapeutic capabilities such as anticancer, anti-inflammatory, antifungal, antibacterial, anticonvulsant, cardioprotective, gastric health, and analgesic effects (50).

Several studies found that cilantro extract delays the onset of PTZ-induced seizures in rats, though they did not describe the mechanism of action nor the active component in cilantro (51, 52). We recently found that a 1% solution of a methanolic extract of cilantro leaves caused a negative shift in the voltage dependence of neuronal KCNQ channels when expressed in *Xenopus* oocytes (53). For KCNQ2/3 heteromers, there was a nearly −17-mV shift in the $V_{0.5activation}$, suggesting that KCNQ2/3 activation is once again underlying the anticonvulsant effects of a traditional botanical medicine, in this case cilantro (Figure 3a).

A screen of several compounds known to be found in cilantro (54) revealed that 100 μM (E)-2-dodecenal causes a similar negative shift in the voltage dependence of KCNQ2/3 heteromers as did cilantro extract (Figure 3b). Additionally, 100 μM (E)-2-dodecenal activated KCNQ2 and KCNQ5, producing approximately −17-mV and −14-mV changes in $V_{0.5activation}$, respectively. KCNQ1 was slightly activated, with an approximately −9-mV

shift in $V_{0.5activation}$, while KCNQ3* (a mutant, A315T, that passes more current to facilitate KCNQ3 studies) exhibited no change in voltage dependence due to (E)-2-dodecenal. (E)-2-dodecenal is highly potent, with an EC_{50} of 60 nM for its augmenting effect on KCNQ2/3 activity at −60 mV. As for GABA, retigabine, MTX, and IVA, (E)-2-dodecenal occupies a binding pocket lined by (human KCNQ2 numbering) W236 and R213 (Figure 3c) and is especially dependent on KCNQ2-R213 for its effects on KCNQ2/3 channels. Interestingly, KCNQ3 is insensitive to (E)-2-dodecenal (53).

The implications of the findings extend beyond the molecular mechanistic understanding of cilantro as a botanical medicine. (E)-2-dodecenal is commonly used as an additive for food flavoring (it gives citrus notes and contributes largely to the distinctive smell and taste of cilantro) and in cosmetics, candles, soaps, and household cleaning products. This fact suggests that we may be exposed on a regular basis to (E)-2-dodecenal levels sufficient to influence KCNQ channel activity.

(E)-2-dodecenal is a 12-carbon fatty aldehyde that has been found to be the primary component (15.6%) of essential oil derived from cilantro leaves (54). Interestingly, it was the only fatty aldehyde tested that activated KCNQ2/3 channels; though structurally very similar, neither 10-, 11-, nor 13-carbon aldehydes were capable of activation, highlighting the remarkable structural specificity of the activation effects for this series of aldehydes (53). Additionally, mice pretreated with (E)-2-dodecenal exhibited a greater than threefold increased latency to first PTZ-induced seizure, while tridecanal, which did not activate KCNQ2/3, had no effect on seizure latency. Once again, these data strongly suggest that KCNQ2/3 activation by (E)-2-dodecenal is at least partially responsible for the anticonvulsant properties seen in cilantro (53).

(E)-2-dodecenal is also found in other plants, most notably culantro (*Eryngium foetidum*), also known as Mexican coriander and fitweed because of its traditional use to counteract seizures, which is native to the Caribbean, Mexico, and Central and South America. (E)-2-dodecenal activation of KCNQ2/3 channels is therefore also a likely mechanistic underpinning for the therapeutic effects of culantro.

HYPOTENSIVE HERBS AND KCNQ5

In modern society, hypertension (high blood pressure) is extremely common, and it is associated with high rates of cardiovascular disease and mortality. In the past, hypertension was referred to as hard pulse disease and was described in records dating back as far as 2600 BCE. In many ancient civilizations, hypertension was treated using venesection, acupuncture, leeches, and herbal remedies (12, 55, 56).

Historically, many herbs have been used to treat hypertension—some of which include plants still in use today both for culinary reasons and for their purported beneficial effects. These plants include lavender, basil, chamomile flower, fennel seed, and *Sophora flavescens* root (Ku Shen) (56). We previously sought to understand if any of these folk medicines might be working via activation of KCNQ5 or KCNQ4/5 channels, which are expressed in vascular smooth muscle and which, when activated, relax the vessels and can help to

lower blood pressure (36-38). Incredibly, 1% methanolic extracts of each of ten purported hypotensive herbs studied activated KCNQ5 channels expressed in *Xenopus* oocytes, though with varying efficacies and potencies, while extracts of herbs that are not thought to lower blood pressure (e.g., spearmint, tarragon, parsley, and wheatgrass) did not (57). Among the most efficacious KCNQ5 openers were fennel seed, lavender, and Ku Shen. Further, none of the ten hypotensive plants exhibited activity with KCNQ2/3, demonstrating some degree of channel isoform selectivity (Figure 4a). KCNQ5-selective channel agonists are very uncommon, with most if not all reported KCNQ activators capable of activating multiple isoforms within KCNQ2–5 and sometimes also KCNQ1.

KCNQ5 is widely expressed in the brain, airway epithelium, retina, and auditory brainstem nuclei and is required for normal vascular, uterine, penile, and gastrointestinal smooth muscle (58-64). It is also capable of forming a heteromeric channel with KCNQ4, which regulates arterial tone at rest (65). The common phenomenon of activation of KCNQ5 by hypotensive plants, and the important role of KCNQ5 and KCNQ4/5 heteromers in the vasculature, suggests that KCNQ5 activation plays a prominent role in the effectiveness of these herbs in treating hypertension.

After screening three alkaloids (aloperine, matrine, and oxymatrine) that had been previously identified in Ku Shen (*S. flavescens* root), we found that aloperine strongly activated KCNQ5, with a nearly −12-mV shift in $V_{0.5activation}$ and a greater than ninefold current increase in the −60-mV tail current. Matrine and oxymatrine had minor impacts on activation. However, the three alkaloids combined summated to nearly perfectly mimic the 1% extract effect on KCNQ5-expressing oocytes. Similar to the extracts themselves, aloperine did not change the activation of KCNQ2/3 heteromers nor homomers of KCNQ2–4 (57) (Figure 4b).

Aloperine has vasodilator and hypotensive properties (66); however, the mechanism was unknown until recently, when we found that preconstricted ex vivo rat blood vessels were KCNQ-dependently relaxed with the addition of aloperine. The vascular relaxation effect of aloperine was blocked by the KCNQ channel inhibitor linopirdine (57). The identification of aloperine as a KCNQ5-specific agonist is potentially exciting, not only for potential hypertension drug development but also for the treatment of KCNQ5 loss-of-function encephalopathies. KCNQ5 haploin-sufficiency causes severe intellectual disability and epileptic encephalopathy (64). Downregulation of KCNQ5 can lead to age-related hearing loss (presbycusis) (67).

We very recently discovered that a 1% methanolic extract of green tea (*Camellia sinensis*) is highly effective at activating KCNQ5 channels at near-resting membrane potentials (>20-fold increase), with much lesser effects on KCNQ2/3; we also found that green tea extract inhibits KCNQ1-KCNE1 channels (68). Black tea was also able to activate KCNQ5. The findings are explained by two polyphenols found in tea. First, epicatechin gallate was discovered to activate KCNQ5 by negative shifting its voltage dependence of activation via interaction with the equivalent arginine at the foot of the voltage sensor (KCNQ5-R212) used by MTX, aloperine, and (E)-2-dodecenal. Epicatechin gallate was isoform-selective, as it did not alter KCNQ2/3 or KCNQ1-KCNE1 activity. Second, epigallocatechin-3-gallate

also activated KCNQ5 and, after heating to at least 35°C (even with subsequent long-term storage refrigeration), was more effective at activating KCNQ5, and it also recapitulated the KCNQ1-KCNE1 inhibitory effects previously found by others (69) and that we observed for whole green tea extract (68). We concluded, based on liquid chromatography mass spectrometry analyses, that heating creates epigallocatechin-3-gallate degradation products that are more KCNQ active than epigallocatechin-3-gallate itself. Both epicatechin gallate and epigallocatechin-3-gallate were able to KCNQ-dependently relax rat mesenteric artery, while epicatechin neither activated KCNQ5 nor relaxed mesenteric artery (68). Effects were within the concentration range of the tea polyphenols found to occur in human plasma following a single cup of black tea (70), supporting the importance of KCNQ5 activation in the ability of tea to lower blood pressure.

QUERCETIN MODULATES SEVERAL KCNQ ISOFORMS VIA AN ATYPICAL MECHANISM

Quercetin is the most commonly consumed flavonoid, as it is found in such a wide variety of food plants. It is predicted that most people consume around 15 mg daily in their diet (71). Although the bioavailability of quercetin in the foods/supplements people take is still not completely understood, numerous studies have begun to look at the benefits of quercetin consumption (71). Capers, the immature flower buds of the caper bush (*Capparis spinosa*) (Figure 5a), are the richest natural source of quercetin (323 mg/100 g), with the caveat that the especially high content is aided by pickling (giving as much as 520 mg/100 g), the form most ingested in, e.g., the United States and United Kingdom (72, 73). The related flavonoid rutin (quercetin-3-*O*-rutinoside) is found in even higher quantities in capers and is converted to quercetin during the pickling process (72, 73) (Figure 5b). Capers have been consumed by people for at least 10,000 years according to archaeological evidence from Syria, Greece, and Israel, and throughout human history, capers have been used for nutrition and medicine (74).

We recently found that quercetin potentiates KCNQ1/KCNE1, KCNQ1/KCNE3, KCNQ2/3, and KCNQ4 activity, though not that of KCNQ5. The lack of effects on KCNQ5 hinted that KCNQ activation by quercetin might be atypical, as KCNQ5 is typically sensitive, and often especially so, to activation by small molecules that also activate other KCNQ isoforms (75). Indeed, mutagenesis and in silico docking studies revealed that quercetin does not occupy the S5/S4–5 binding site on KCNQ channels that accommodates GABA and, e.g., retigabine in neuronal KCNQ isoforms and a range of plant secondary metabolites in multiple KCNQ isoforms. Instead, quercetin is predicted in in silico docking analyses to sit atop the voltage sensors interacting with arginine residues R228 and R231 (human KCNQ1 numbering), a premise supported by mutagenesis and electrophysiology studies (Figure 5c). Interestingly, there also appears to be a quercetin binding location near the pore, predicted by in silico docking, and reinforced by mutagenesis and electrophysiology data, to require F340 in the S6 segment of KCNQ1 (75) (Figure 5d). We previously found that F340 acts as a hub controlling KCNQ1 gating processes, providing a particularly influential site for ligands that have the capability to interact with it (76). This may explain why quercetin accelerated both the activation and inactivation of homomeric KCNQ1 (75).

POTENTIAL QUERCETIN-KCNQ INTERACTION IMPACTS ON HUMAN HEALTH

Research is ongoing into the potential benefits of capers and/or quercetin in a range of disorders, including cancer, diabetes, erectile dysfunction, hearing loss, cardiovascular and gastrointestinal diseases, inflammatory disorders, and parasitic infections (77, 78). Potential roles for quercetin modulation of KCNQ channels in reported beneficial effects are discussed below.

KCNQ4 is expressed in outer hair cells of the inner ear and in auditory neurons and is essential for normal hearing. *KCNQ4* loss-of-function mutations in humans and knockout in mice cause nonsyndromic progressive deafness characterized by degeneration of outer hair cells, probably arising from chronic depolarization (39, 79, 80). Loss-of-function mutations in human *KCNE1* or *KCNQ1* (or knockout in mice) can result in profound sensorineural deafness and the cardiac and auditory Jervell and Lange-Nielsen syndrome (homozygous or compound heterozygous mutations). The auditory dysfunction is characterized by a loss of K^+ secretion by the stria vascularis of the cochlea and by cells in the vestibular epithelium (a process normally carried out by KCNQ1/KCNE1 channels), leading to hair cell death (81-84). Each of these phenotypes would hypothetically be correctable by drugs that increase KCNQ4 and/or KCNQ1/KCNE1 currents in the ear (i.e., by acting on channels expressed at the cell surface that are dysfunctional), such as occurs in vitro with quercetin. Interestingly, quercetin was recently found to protect against inner ear hair cell loss in two different animal models (85). KCNQ4 is also found in bladder smooth muscle and may be a target to control bladder detrusor muscle activity (86, 87). Quercetin has been found to relieve symptoms of cystitis, an inflammation of the bladder most commonly linked to urinary tract infection (88).

High-dose quercetin (i.e., when patients are given >500 mg/day) was recently shown, in a meta-analysis of randomized controlled human trials, to reduce blood pressure by 4.5 mm Hg (89). KCNQ4 is expressed in vascular smooth muscle (probably in heteromeric KCNQ4/KCNQ5/KCNE4 complexes), and its activation relaxes vascular smooth muscle (90-94), suggesting one possible mechanism for the hypotensive effects of quercetin. KCNQ3, KCNQ4, and KCNQ5 are expressed in penile arteries and corpus cavernosum, and KCNQ1 is also found in the latter (90). It is therefore of interest that quercetin was found to be beneficial in at least two different rat models of arterial erectile dysfunction (95, 96).

KCNQ1 is required for normal function of the pancreas in complexes with one or more KCNE subunit isoforms. Knockout of mouse *Kcnq1* or *Kcne2* alters insulin sensitivity and in the case of *Kcne2* causes type 2 diabetes mellitus (T2D) (97, 98). Indeed, human *KCNQ1* sequence variation is widely linked to T2D (99, 100). Quercetin was previously shown to ameliorate streptozotocin-induced β cell damage and oxidative stress in rat pancreas (101), and it shows promise as an antidiabetic agent, especially in conjunction with other plant compounds such as resveratrol (102).

KCNQ1 also co-assembles with KCNE subunits throughout the gastrointestinal tract: KCNE2 in the stomach and KCNE3 in the colon, intestine, and duodenum (21).

Quercetin enhances KCNQ1/KCNE3 currents by superimposing a voltage-dependent current component on the constitutive component. Interestingly, low human KCNQ1 expression correlates with stage II and III disease recurrence and poor overall colon cancer survival rates (103, 104). Quercetin was recently shown to induce human colon cancer cell apoptosis (105) and has shown promise in animal models of colorectal cancer (106). Consistent with the finding that quercetin augments KCNQ1/KCNE3 activity (75), quercetin was previously found to activate Cl^- secretion by activating a basolateral K^+ current in rat colon, although the molecular correlate was not identified (107).

CONCLUSION

Plants continue to play an undeniably significant role in medicine. Studying the molecular mechanisms of action of plant extracts used in botanical folk medicines and their constituents helps us develop a deeper understanding of how their consumption has led to therapeutic results, increases our wonder at the ability of ancient cultures to discover natural medicines in the world around them, and helps document and acknowledge the knowledge of our ancestors. It also reinforces the importance of preserving our native flora and fauna, and the habitats they require to thrive, for the sake of both the natural world and the human race. Study of the mechanisms underlying folk medicines also allows us to develop the compounds within them, and their structures, as a basis for synthetic medicines. There are still many unknown therapeutic possibilities of plants that require much more research.

Recent studies from the lab of the authors, and other groups, have identified the functionally versatile pore-forming α subunits of the KCNQ subfamily of Kv channels as just one subclass of targets for the beneficial effects of plant secondary metabolites. Nevertheless, as KCNQ channels are ubiquitously expressed, versatile in function, and physiologically influential, they may emerge as an important target subset. Given that Kv channels in general are viewed as a highly underutilized class of drug target, it is hoped that a fuller understanding of the role of KCNQ channels as a conduit for the benefits of traditional folk medicines will help both open up their use as drug targets in a broader sense and steer the use of traditional medicines and their components to personalized therapeutic approaches guided by pharmacogenetics.

ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from the National Institutes of Health, National Institute of General Medical Sciences (GM130377 to G.WA.), and National Institute of Neurological Disorders and Stroke (T32NS045540 to K.E.R.). We thank Bo Abbott for botanical photography.

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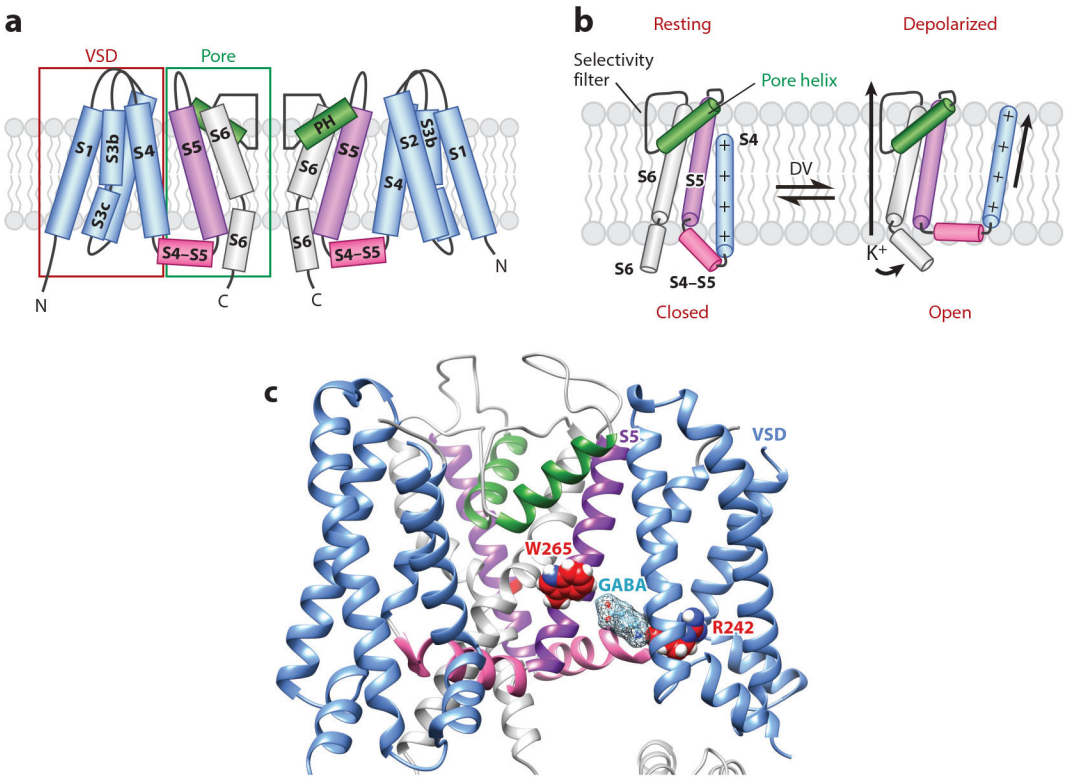

Figure 1.

KCNQ channels and their γ-aminobutyric acid (GABA) binding site. (*a*) Diagram of the transmembrane domains encoded by *KCNQ* genes, highlighting the voltage-sensing domain (VSD) (S1–S4, *red box*) and pore module (S5–S6, *green box*). (*b*) Diagram showing how membrane depolarization causes the channel to open, allowing for potassium efflux. (*c*) SwissDock (108, 109) model visualized in UCSF Chimera showing the predicted docking position of GABA in a model of KCNQ3 (human KCNQ3 numbering) (33). Figure adapted with permission from Reference 20.

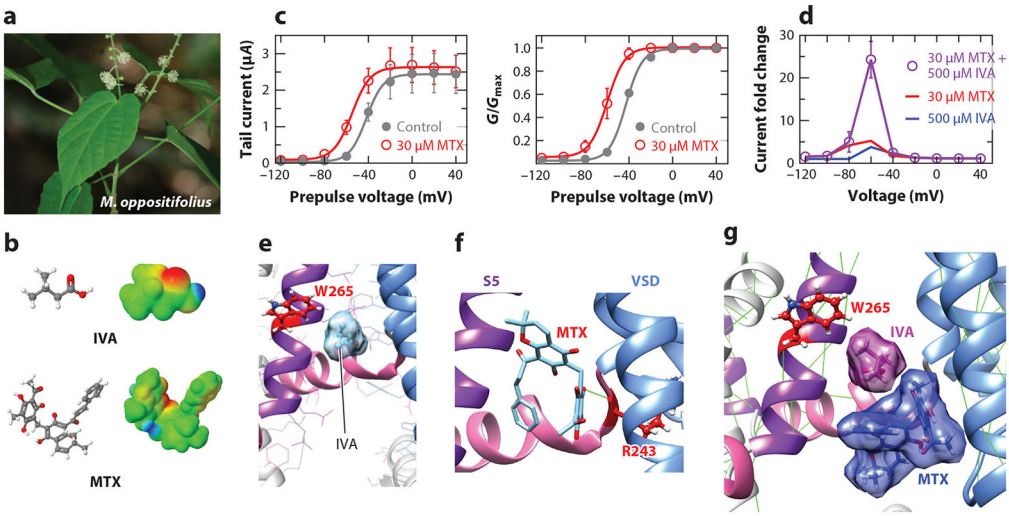

Figure 2.

Mallotus oppositifolius activates KCNQ2/3 channels. (*a*) *M. oppositifolius* plant. Photo provided by E. Bidault, Tropicos, Missouri Botanical Garden (http://tropicos.org/Image/100521734) (CC BY-NC-ND 3.0). (*b*) Structure (*left*) and electrostatic surface potential (*right*; plotted in Jmol) (negative, *red*; positive, *blue*) of isovaleric acid (IVA) and mallotoxin (MTX). (*c*) MTX effects on KCNQ2/3. Raw tail (*left*) and normalized tail (*right*) current data are shown for control (*gray*) and with the addition of 30 μM MTX (*red*). (*d*) Fold change in raw KCNQ2/3 tail current versus prepulse voltage for the combinations indicated. (*e*) SwissDock-predicted docking pose of IVA in a neuronal KCNQ channel (human KCNQ3 numbering). (*f*) SwissDock-predicted docking pose of MTX in KCNQ1 (human KCNQ1 numbering). (*g*) SwissDock-predicted docking poses of IVA and MTX simultaneously in a neuronal KCNQ channel (human KCNQ3 numbering). Panels *b–g* adapted with permission from Reference 44.

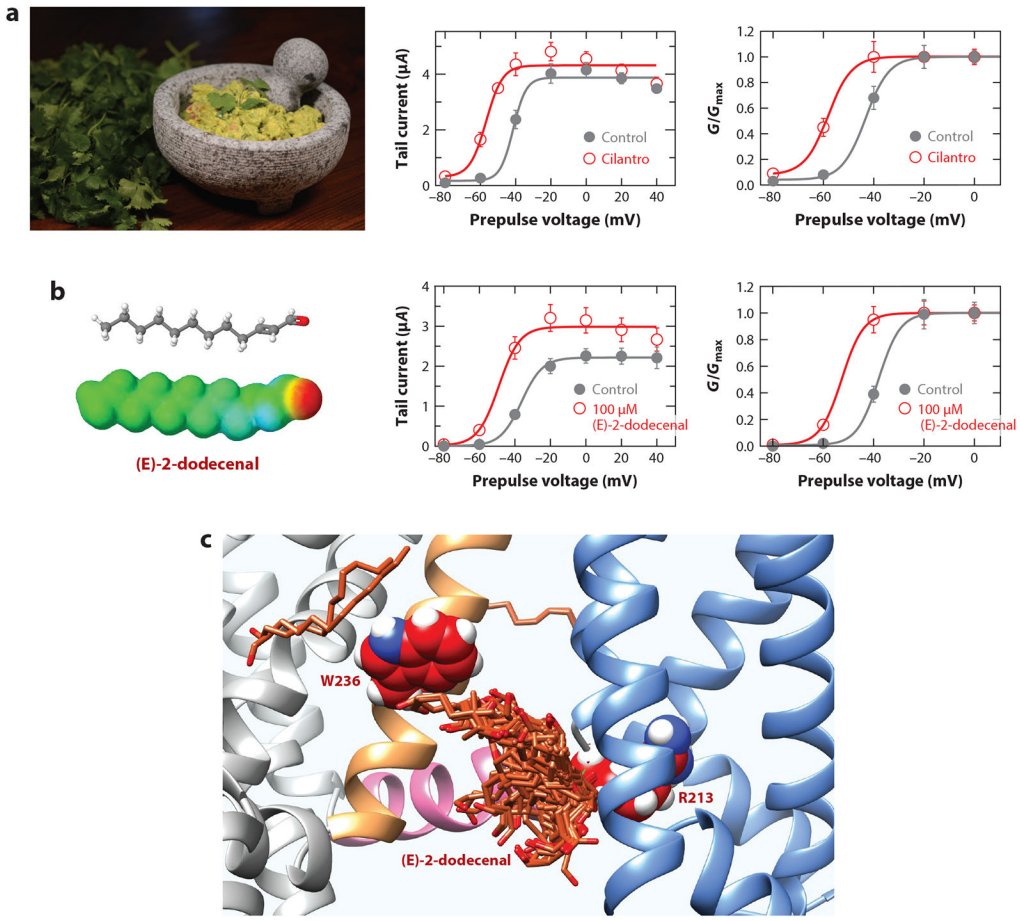

Figure 3.

(E)-2-dodecenal from cilantro activates KCNQ2/3 channels. (*a*) Image of cilantro (*left*), and raw (*middle*) and normalized (*right*) KCNQ2/3 tail current data for the control (*gray*) and with the addition of 1% cilantro extract (*red*). Photo provided by Bo Abbott and used with permission; graphs adapted with permission from Reference 53. (*b*, *left*) (E)-2-dodecenal structure (*upper*) and electrostatic surface potential (*lower*; plotted in Jmol) (negative, *red*; positive, *blue*). Raw (*middle*) and normalized (*right*) KCNQ2/3 tail current data for the control (*gray*) and with the addition of 100 μM (E)-2-dodecenal (*red*). Graphs adapted with permission from Reference 53. (*c*) SwissDock (108, 109) prediction of (E)-2-dodecenal docking to KCNQ2. Panel *c* adapted with permission from Reference 20.

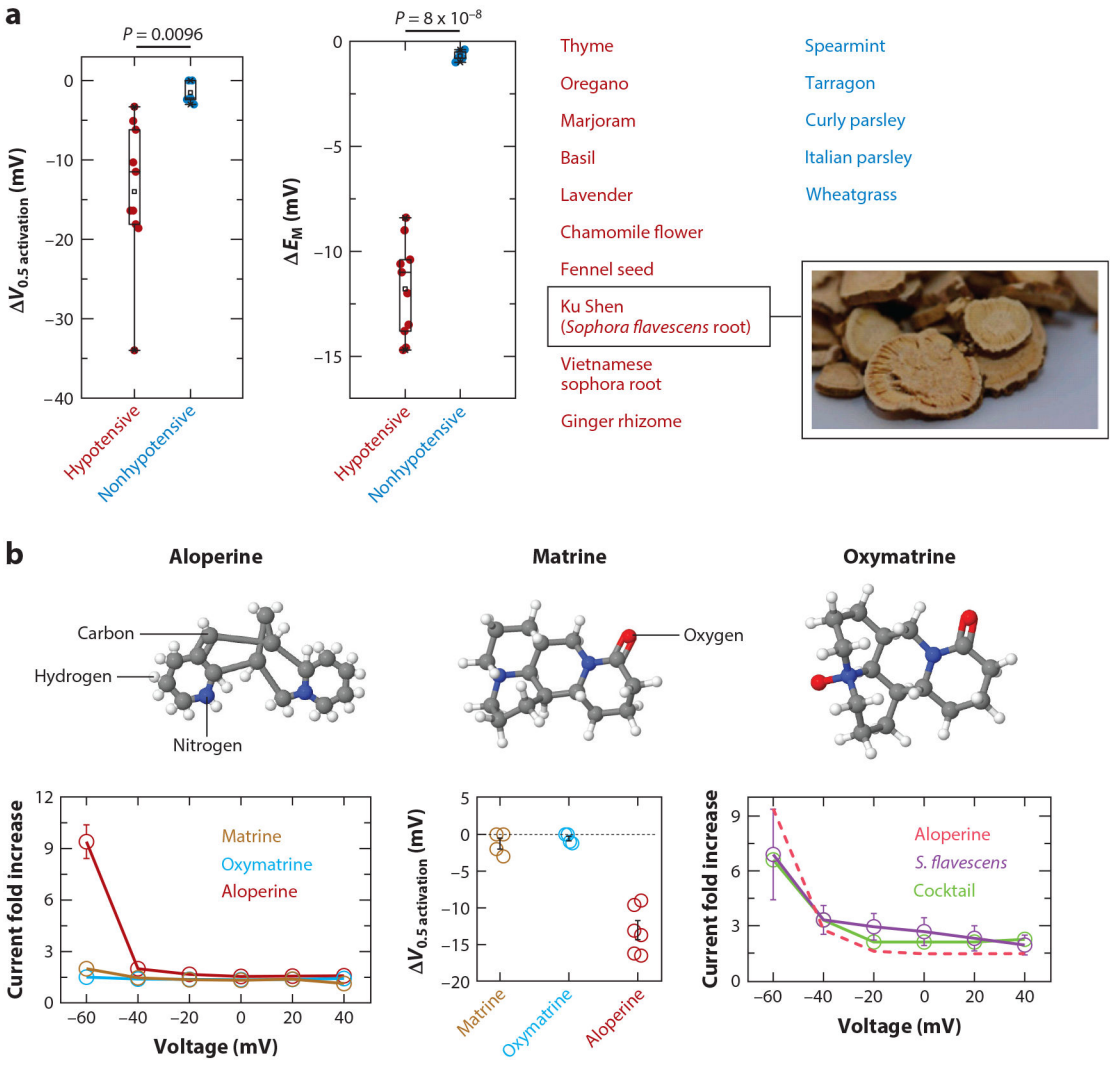

Figure 4.

Hypotensive herbs activate KCNQ5. (*a*) Effects of the listed hypotensive (*red*) and nonhypotensive (*blue*) herb extracts on KCNQ5 activity and KCNQ5-induced shifts in resting membrane potential (ΔE_M) (expressed in *Xenopus* oocytes). Panel *a* adapted with permission from Reference 57, photo of Ku Shen (*Sophora flavescens*) provided by Bo Abbott and used with permission. (*b*) Structures (*top*) and effects of the Ku Shen components aloperine, matrine, and oxymatrine on KCNQ5 current (*bottom left*), change in midpoint voltage of activation (*bottom middle*), and in combination (cocktail) versus aloperine alone or Ku Shen extract (*bottom right*). Panel *b* adapted with permission from Reference 57.

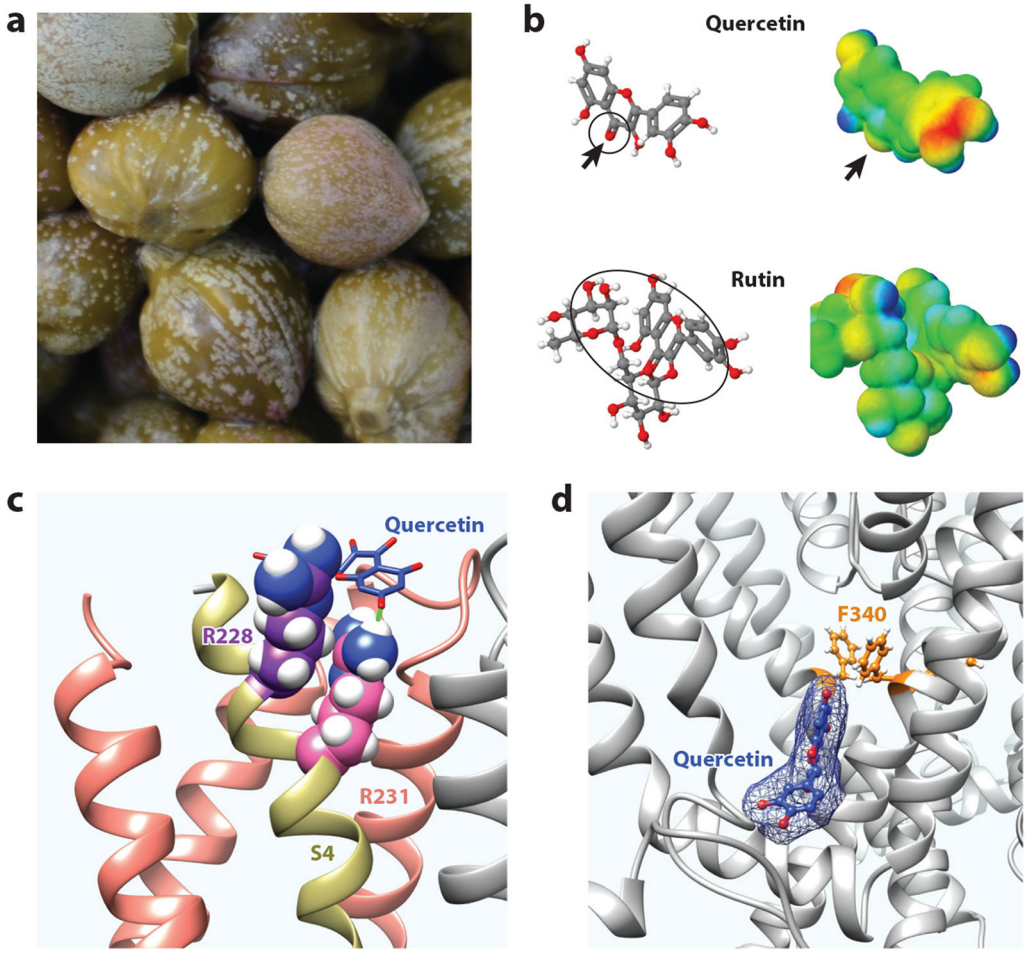

Figure 5.

Quercetin activates KCNQ channels. (*a*) Image of pickled capers, the food richest in quercetin. Photo provided by Bo Abbott and used with permission. (*b*) The structures (*left*) and electrostatic surface potential (*right*; plotted in Jmol) (negative, *red*; positive, *blue*) of quercetin and rutin. Arrows indicate a carbonyl group. The quercetin moiety is circled in the rutin structure. (*c*) SwissDock (108, 109) prediction of quercetin binding to the top of KCNQ1-S4. (*d*) SwissDock prediction of quercetin binding to KCNQ1-F340. Panels *b–d* adapted with permission from Reference 75.