Piper Betel Leaf: A Reservoir of Potential Xenohormetic Nutraceuticals with Cancer-Fighting Properties

Sushma R. Gundala and Ritu Aneja

Abstract

Plants contain a much greater diversity of bioactive compounds than any man-made chemical library. Heart-shaped Piper betel leaves are magnificent reservoirs of phenolic compounds with antiproliferative, antimutagenic, antibacterial, and antioxidant properties. Widely consumed in South Asian countries, the glossy leaf contains a multitude of biophenolics such as hydroxychavicol, eugenol, chavibetol, and piperols. Convincing data underscore the remarkable chemotherapeutic and chemopreventive potential of betel leaves against a variety of cancer types. The leaf constituents modulate an extensive array of signaling molecules such as transcription factors as well as reactive oxygen species (ROS) to control multiple nodes of various cellular proliferation and death pathways. Herein, we provide an overall perspective on the cancer-fighting benefits of the phenolic phytochemicals in betel leaves and a comprehensive overview of the mechanisms responsive to dose-driven ROS-mediated signaling cascades conscripted by bioactive phenolics to confer chemotherapeutic and chemopreventive advantages. Intriguingly, these ROS-triggered responses are contextual and may either elicit a protective xenohormetic antioxidant response to premalignant cells to constitute a chemopreventive effect or generate a curative chemotherapeutic response by pro-oxidatively augmenting the constitutively elevated ROS levels in cancer cells to tip the balance in favor of selective apoptosis induction in cancer cells while sparing normal ones. In conclusion, this review provides an update on how distinct ROS levels exist in normal versus cancer cells and how these levels can be strategically modulated and exploited for therapeutic gains. We emphasize the yet untapped potential of the evergreen vine, betel leaf, for chemopreventive and chemotherapeutic management of cancer.

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Introduction

Mankind has relied on plants as a source of medicine for eons. Unsurprisingly, plants contain a much greater diversity of bioactive compounds than any known man-made chemical library. Even today, as much as 80% of the population in developing countries banks on medicinal plants as their only affordable source of medication (1). No wonder nature has been a matchless source of multicomponent concoctions and single compounds ranging from simple phenolics to complex alkaloids that have been developed over the millennia to modulate various cellular mechanisms for therapeutic gains. The myriad benefits of these natural products, which actually emerged because of the interactions among plants and their surrounding environment to enhance survival, are prodigious and well appreciated in every aspect of life. Furthermore, the wide variety of compounds like vitamins, carotenoids, flavonoids, isothiocyanates, sulfides, thiols, phenols, and alkaloids in plant extracts have helped cure and/or manage several chronic conditions like diabetes, hepatitis, arthritis, cardiovascular, cerebrovascular diseases, and cancer. Cancer, a malicious disease that gripped mankind since its dawn in early in fourth century BC (2), has been an alarmingly increasing cause of death worldwide over the past 20 years. Continuing research efforts to identify a cure for cancer have met with limited success, and the war against this deadly neoplasm is growing stronger by the day. Most pharmaceutical compositions of various purified compounds and crude chemopreventive and chemotherapeutic formulations today are from the inexhaustible chemical inventory of plants.

Current chemotherapy: one size does not fit all

The greatest impact of plant-derived drugs has been in the anticancer area, wherein the development of plant-derived drugs such as taxol, vinblastine, vincristine, and camptothecin has proven to be a boon in the treatment of some of the deadliest cancers. This perhaps fueled the notion that single constituents of medicinal plants dictate their pharmacologic activity. Although this paradigm has resulted in several outstanding synthetic drug molecules and many more entering the pipeline of clinical trials, it is rather dismaying that about 60% of drug candidates either fail late-stage
clinical development or shortly after entering the market due to debilitating toxicity, limited efficacy, or emergence of drug resistance (3). One obvious explanation for these failures is that disease pathogenesis involves dysregulation of multiple molecular pathways and thus the “silver bullet” approach of mononotargeting yields limited efficacy. Paradoxically, the multifactorial nature of cancer requires a pleiotropic approach wherein a whole plant extract, a multicomponent concoction, or a fractionated mixture of phytochemicals or even a single agent can simultaneously hit multiple targets in consecutive or parallel pathways to achieve optimal clinical efficacy.

**Plant extracts: phytochemical potions with miraculous medicinal powers**

Owing to the unmistakable promise of herbal medications, there is an ever-increasing quest for new plants that could possibly hold the key to prevent or eliminate this dreaded disease by conferring superior chemopreventive or chemotherapeutic properties. The secondary metabolites produced by plants, referred to as phytochemicals are often plant stress signaling molecules, which have been identified to resist stress, fight disease, and improve longevity in animals consuming them, a phenomenon known as *xenohormesis* (4–7). Indeed the phytochemicals present in fruits and vegetables (e.g., carotenoids, polyphenolics, anthocyanins, terpenes, alkaloids) are functionally pleiotropic; they possess multiple intracellular targets, affecting different cell signaling cascades usually altered in cancer cells with limited toxicity to normal cells. However, the host of disease-combating chemicals is not limited to fruits and vegetables, but is widely spread across the major ingredients of our cuisines, spices, and herbs. The nutraceuticals derived from spices and herbs have also been shown to modulate multiple targets, including the transcription factors (NF-κB, Nrf2, hypoxia-inducible factor-1α), kinases, and inflammation markers (8). However, there still exist several unexplored exotic condiments with promising disease-fighting potential.

**Some plants have it all: the versatile pharmacopoeia of Piper betel leaves**

Although known from ancient times, scientific interest in *Piper betel*, an evergreen vine, was restricted owing to misconceptions largely due to the consumption of betel quid, a combination of betel leaf with areca nut, slaked lime, and tobacco, which is a storehouse of several carcinogens and has been linked to the development of oral cancer (9–11). Recent years have seen a rekindled interest in pursuing this plant especially betel leaves, are used in traditional medicine for treatment of several conditions such as abscesses, constipation, conjunctivitis, itches, rheumatism, abrasions, and many more (14, 15). Although the roots of *Piper betel* have served as alternative oral contraceptives, the oil obtained from betel leaves has bactericidal action (13). Consumption of betel leaves has also been known to stimulate feelings of well-being, amplified salivation, perspiration, alertness and a sense of increased energy, and warmth (13). A meticulous evaluation of the leaf as a whole and its constituents has yielded many more medicinal properties such as antifungal, antimicrobial, wound healing, antioxidant, antimutagenic, and chemopreventive activities (refs. 12, 16; Fig. 1).

Here below, we attempt to synopsize existing knowledge on the cancer-fighting properties of betel leaf and its phytochemical constituents, and present an overview of cellular nuances driven by phenolic phytochemicals that trigger reactive oxygen species (ROS)-mediated signaling circuits to launch a two-pronged offensive; one that underlies chemopreventative benefits produced by a potential xenohormetic response which fortifies the antioxidant defense system in premalignant cells, and the other that undergirds chemotherapeutic efficacy due to the induction of apoptosis by overwhelming the cellular ROS content.

**Betel leaves: abundant repositories of cancer-fighting phytochemicals**

An enriched source of calcium, vitamin C, niacin, thiamine, carotene, and riboflavin (17), betel leaves are clearly associated with nutritive benefits. Thus, referring to them as betel nutraceuticals is supported and well reasoned. Other betel phytochemicals include allylpyrocathecol (APC; 2-hydroxychavicol), 4-hydroxy catechol, β-caryophyllene, methyl eugenol, carotenes, starch, diastases, and an essential oil containing hydroxychavicol (18, 19). Hydroxychavicol, a phenolic compound quantitatively present at approximately 26% in betel leaves, has been shown to exert antiproliferative activity in prostate cancer (20). Hydroxychavicol has also been shown to impede cell-cycle progression of prostate cancer and oral KB carcinoma cells (20–22). Several reports indicate hydroxychavicol as an antimutagenic agent (12, 23) as well as an effective inhibitor of cyclooxygenase (COX), platelet calcium signaling, and thromboxane B2 production (21). Other studies suggest...
that hydroxychavicol also known as APC possesses anti-ulcerogenic activity (24) and has been shown to alleviate indomethacin-induced stomach ulceration leading to gastric cancer (25). Hydroxychavicol also inhibits inflammatory response molecules like inducible nitric oxide synthase and COX-2, which are known to enhance tumor growth by downregulation of the NF-κB pathway (24). Chavibetol (CHV), along with hydroxychavicol, acts as a radioprotector (25), and exhibits substantial immunomodulatory and free radical scavenging activities (25). We have shown that CHV synergizes with hydroxychavicol to exert antiproliferative activity against human prostate cancer PC-3 cells (20). Betel leaf contains large amounts of safrole, which is rapidly degraded in the human body into dihydroxychavicol and eugenol, the antimutagenic agents, which are then excreted via the urine (26, 27). Chlorogenic acid (ChA), another active ingredient isolated from betel leaves, has been reported to eliminate cancerous cells without harming normal cells, unlike most conventional chemotherapeutics (13). In addition to cytotoxic and antimutagenic properties, the betel bioactive constituents have been studied for their oxidative properties (ref. 28; Fig. 1). For example, high hydroxychavicol concentrations provoke its pro-oxidant behavior as demonstrated by induction of oxidative damage in liver cancer cells (29). Interestingly, hydroxychavicol was found to be a potent antioxidant at lower doses in oral KB carcinoma, whereas high doses led to apoptosis induction by increasing ROS levels (22).

Thus, similar to other plant-derived phenolic phytochemicals, bioactive betel constituents as single agents exert
paradoxical anti- and pro-oxidant activities contextually. Given that plant extracts are invariably multicomponent, their activities can perhaps be more representative of an averaged "profile" of anti- and pro-oxidant behavior, which may be an additive summation or an even more complex synergistic interaction among the individual components. There are a lot of conflicting reports on ROS-quenching antioxidant mechanisms and ROS-generating pro-oxidant ones that are believed to majorly drive the chemopreventive and chemotherapeutic agenda in preneoplastic and neoplastic cells, respectively. This calls into question the unambiguity in defining a framework for an accurate assessment of the chemopreventive and/or chemotherapeutic contributions of these two-faced phytochemicals. Here below, we revisit the paradoxical roles of plant phytochemicals in general to better comprehend the versatility of the phenolic functionality in betel phytochemicals as a double-edged sword.

Chemotherapeutic (toxic pro-oxidant) and chemopreventive (protective antioxidant) activities of plant phytochemicals: two healthful sides of the same coin

The most well studied health-promoting phytochemicals (epigallocatechin gallate, curcumin, resveratrol, quercetin, caffeic acid, rutin, gingerols, ChA, etc.) belong to the phenol superfamily. In particular, for betel leaves, the versatile phenolic compounds include hydroxychavicol, eugenol, CHV, piperol, and ChA, and can also serve as examples of secondary metabolites. These compounds merit a special mention, as they are the primary defense molecules of plants and have protected them during evolution. In addition, these phenolics have "chemically" contributed to maintain an ecological equilibrium between plants and other living organisms feeding on them, including us, humans. The magnanimous nature of these betel leaf compounds can be attributed to the inherent physicochemical properties packaged within the phenol functional group. The phenol groups in plants offer remarkable molecular flexibility resulting in an apparent dichotomy associated with the versatile phenolic function. Most betel constituents are composed of an amphiphilic moiety with the hydrophobic nature of its planar aromatic nucleus coupled with the hydrophilic character of its polar hydroxyl group, which can act as a hydrogen-bond donor or as an acceptor. The presence of flavonoids, polyphenols, terpenoids, and alkaloids (30) in betel leaves makes them a remarkable sink as well as a source for ROS thus conferring antioxidant as well as pro-oxidant traits to the leaf extract. As alluded to earlier, the paradoxical traits (antioxidant and pro-oxidant) of betel nutraceuticals empower them to offer both chemotherapeutic (cancer cells) and chemopreventive benefits (prenalignant cells), albeit through different mechanisms (8, 31–34). Once preneoplastic cells undergo malignant transformation into cancer cells, they can perhaps only be eliminated through chemotherapeutic strategies, as upon becoming cancerous, these cells have surpassed their amenability to chemopreventive measures.

Unlike normal cells, cancer cells owing to their enhanced metabolic activity have constitutively higher levels of ROS, which spawn a persistent pro-oxidative environment (35–37). Nonetheless, cancer cells despite high ROS concentrations, survive by adapting to the increased oxidative stress by upregulating prosurvival mechanisms and altering their antioxidant systems (Fig. 2).

Normal cells, however, operate within an "optimal window" to maintain a redox balance between generation and elimination of free radicals, but also possess a robust capacity to tolerate a sizeable fluctuation in ROS levels. In contrast, cancer cells with already high basal ROS levels have a much "narrower" window to endure elevations in ROS levels. This "vulnerability" or susceptibility of cancer cells can be exploited by whole betel extract (or its constituent phytochemicals) to selectively kill cancer cells by augmenting ROS levels beyond the toxic threshold that cancer cells can withstand (Fig. 3). Nevertheless, a "similar-scaled" pro-oxidant

![Figure 2. This figure represents the fate of cancer cells under varying ROS levels. Cancer cells having moderate levels of ROS tend to adapt to the stress conditions and show enhanced expression of prosurvival molecules. When betel nutraceuticals interfere with this situation, causing the moderate ROS levels to increase over the threshold, the cancer cells can no longer withstand the oxidative stress and thus are killed via various possible mechanisms (12, 22, 27, 29, 37, 38, 45, 47, 62, 64–66).](image-url)
Betel nutraceuticals offer chemopreventive benefits: potential "xenohormetics"

A rekindled scientific interest in betel leaves has spurred several studies focused on investigating the chemopreventive properties of betel leaves. More evidence to support the potential benefits of betel leaves came from the identification of antimutagenic properties of betel leaf constituents, especially hydroxychavicol, which repressed oral carcinogenesis induced by standard mutagens like benzo[a]pyrene and dimethylbenz[a]anthracene in hamsters (48), and tobacco-specific nitrosamines like 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN) in mice (49, 50), when betel leaf extract was topically applied. In addition, β-carotene and α-tocopherol of betel leaf extract caused prolonged latency, regression of established tumors, and decrease in tumor incidence and tumor size in Syrian hamsters exposed to another mutagen named acetoxymethyl nitrosamine, thus indicating a strong chemopreventive effect of betel leaves (51).

Furthermore, studies involving effects of betel leaves against 7,12-dimethylbenz[a]anthracene (DMBA)-induced breast cancer provided remarkable cues emphasizing their chemopreventive efficacy. It was observed that when betel leaf extract was fed to rats bearing mammary tumors in the initiation phase, the tumor growth was prevented, while rats with fully developed mammary tumors failed to show any reduction/inhibition in tumor growth (52, 53). We have recently reported that betel leaf extract exhibits significant efficacy in inhibiting growth of prostate cancer xenografts (20). These studies generate compelling foregrounds to warrant future investigation of chemopreventive efficacy of betel leaves and/or bioactive betel leaf constituents in appropriate animal models.

Insights into the mechanistic actions of betel leaf constituents were obtained from several investigations that focused on the effect of betel leaf on gastric carcinomas. For instance, eugenol, hydroxychavicol, β-carotene, and α-tocopherol were identified to be key players in suppressing benzo[a]pyrene-induced neoplasms of the gut in mice, when betel leaf extract was mixed with drinking water (49). Eugenol was further proven to be inducing intrinsic apoptosis in Wistar rats bearing N-methyl-N-nitro-N-nitrosoguanidine-induced tumors, and decrease in tumor incidence and tumor size in Syrian hamsters exposed to another mutagen named acetoxymethyl nitrosamine, thus indicating a strong chemopreventive effect of betel leaves (51).

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induced gastric cancer by modulating Bcl-2 family proteins along with Apaf-1, cytochrome C, and caspases (54). Furthermore, studies involving specific carcinogens like DMBA, which are well known to cause skin cancer, revealed the significance of \( \beta \)-carotene and \( \alpha \)-tocopherol in inhibiting the onset of tumors in mice. Simultaneously, although hydroxychavicol exhibited the same response, but to a greater extent, eugenol, however, could only offer limited protection against DMBA-induced skin tumors (55). Other studies by Azuine and colleagues suggested that eugenol in the betel leaves exhibited specific antiproliferative activity while partially triggering apoptosis (56) along with eliciting superoxide formation, lipid peroxidation, and radical scavenging activity, thus illustrating its antioxidant effects (57). Eugenol was also shown to hinder the upstream signaling molecule NF-\( \kappa \)B, a key player in regulating the expression of genes controlling cell proliferation and survival (57).

Despite the existence of strong evidence to demonstrate that betel phytochemicals exert a diverse spectrum of beneficial protective and curative effects in various disease models, there are several perplexing questions that await persuasive answers—How can the same polyphenolic phytochemical (such as hydroxychavicol from betel leaf) 'prevent' cancer by exercising chemopreventive strategies as well as offer 'treatment' by enforcing curative commands for therapeutic gains? How can the long-accepted antioxidant-free radical quenching/scavenging properties of phenols explain their chemopreventive and/or chemotherapeutic benefits of betel leaves? How can we correlate efficacy of these phenols with their antioxidant capacity?

We have alluded to in the above section how polyphenolic compounds in whole betel extract with their biophysicochemical "flexibility" can tip the redox balance in favor of death in cancer cells by taking advantage of their inherently higher ROS levels, which turns out to be their "Achilles heel." Nevertheless, it is difficult to reconcile several of these questions in the chemopreventive context in the absence of a unifying new paradigm called "xenohormesis," which is gaining momentum. This hypothesis assumes that polyphenols were synthesized by common ancestors of plants and animals (58). Despite the evolutionary divergence of the respective kingdoms, it is intriguing that many crucial mammalian enzymes and receptors have been conserved which can be regulated and modulated by plant-produced phytochemicals.

Paramount interest centers on the belief that adverse environmental conditions or stress induce the synthesis of phytochemicals, including polyphenols, in plants. Interestingly, when ingested by humans, these phytochemicals upregulate the pathways that provide stress resistance in animals (Fig. 4). Conceivably, this suggests that humans that consume phytochemicals via plant-based foods have sensing mechanisms (enzymes/receptors) to perceive these chemical cues and elicit beneficial responses that enhance the well-being of humans thus imparting overall health benefits. This phenomenon has been brilliantly termed as "xenohormesis" by Howitz and Sinclair fairly recently in 2008, wherein xenos, is the Greek word for stranger, and hormesis, the term for health benefits (58). In simplistic terms, it is health benefits conferred by a stranger! We envision that ingestion of
phytochemicals causes the body to be tricked into believing that it is under some kind of stress, which triggers a system-wide response to combat stress. While normally, the presence of a handful of initiated or premalignant cells would not be able to trigger a sufficiently strong signal for the body to perceive and respond to, phytochemicals may place the system on "high-alert" and stimulate a heightened stress response that could effectively eliminate initiated or premalignant cells thus emphasizing the workings of plant phytochemicals in the chemopreventive context (Fig. 4).

The polyphenolic redox manipulating phytochemicals commonly display an aromatic core with 1,2-hydroxyl groups, which are found in hydroxychavicol and ChA, or a hydroxyl group and neighboring methyl ether like in eugenol and CHV (Fig. 5). These groups have been shown to act as an electron acceptor or hydrogen atom donor and quench the existing ROS and thus prevent the cell from transforming into a cancerous entity. When present in appropriate concentrations, these powerful phytochemicals act as antioxidants. It has been well described throughout the literature that phenolic compounds exist as excellent electron acceptors due to the resonance stabilization of the radical structure and an excellent hydrogen atom donor for similar stabilization of the resulting oxyanion. Furthermore, the electrophilic reactive oxygen quenchers like ChA and curcumin contain a Michael acceptor enone system shown by the α-, β-unsaturated ketone and maintain the effective ROS manipulating system of the dihydroxyl groups.

On the other hand, it is well studied that plant polyphenols containing catechol and/or pyrogallol moieties can also exert pro-oxidant properties, by reducing iron (III) or copper (II) ions that they chelate. Furthermore, the ortho-hydroxyphenoxy radical produced from the oxidation of a catechol/pyrogallol moiety can also react with a second free-radical species, including \( \cdot \text{O}_2 \), to afford oxidizing orthoquinones and \( \text{O}_2^- \) (59). Because of these reactions, the catecholic betel phenolic compounds like hydroxychavicol and ChA (Fig. 5) induce DNA breakage in the presence of \( \cdot \text{O}_2 \) and iron or copper species, thus leading to death.

The xenohormetic process thus fills the gaps in knowledge on the cancer preventative benefits of plant-based phytochemicals in addition to their roles to kill transformed cancer cells. The xenohormesis phenomenon aids to comprehend the basis of the chemopreventive potential of these betel phytochemicals that “prevent” carcinogenesis and intervene early on in the malignant transformation process. Thus, we believe that it is not unreasonable to include betel phytochemicals endowed with “magical” health imparting...
powers in the armamentarium of the known “xenohormetic” molecules.

In the light of these observations, we may rationalize that in initiated cells, a mild stress induced by betel nutraceuticals, causes the activation of the Nrf2 circuit encouraging the expression of endogenous antioxidants and other cytoprotective genes, which generate a xenohormesis-mediated chemopreventive response. Although extensive data from several in vivo studies demonstrate the chemopreventive efficacy of betel leaf and its constituents, the paucity of supporting clinical data demands an urgent need for strategic exploration of these effects upon daily consumption in humans.

**Health in harmony: synergy among betel nutraceuticals**

The complexity of phytochemicals in their natural forms in plant-based foods precludes a definitive conclusion about their mechanisms of action. However, the existence of synergistic interactions have been long known and linked to the activity of whole foods. The chemotherapeutic and chemopreventive properties of betel leaf and its constituents spur the need for examining and identifying the fraction and constituents thereof, which contribute to the remarkable efficacy. We have recently reported that the least polar fraction, F2, of betel leaf extract exhibited the highest antiproliferative activity when tested against human prostate cancer, PC-3 cells (20). F2 was identified to be consisting of hydroxychavicol and CHV along with other unknown phytochemicals, and hydroxychavicol was found to be the major contributor of betel leaf extract efficacy. Interestingly, this study suggested a possible synergy among F2 constituents but additional in vivo work, including pharmacokinetic evaluations, is warranted to draw conclusions on the potential usefulness of the subfractions or single agents for chemopreventive or therapeutic goals.

Considering the potential synergistic interactions among betel leaf constituents and the remarkable in vivo tumor growth inhibitory dose of whole betel leaf extract in mice bearing human prostate cancer (400 mg/kg body weight; ref. 20), correlations to human health benefits can be obtained. Allometric scaling calculations suggest that upon extrapolation of mice data to humans (60), the approximate human equivalent dose of whole betel leaf extract was found to be approximately 32 mg/kg body weight, which translates to approximately 2.2 g for a 70-kg adult. Furthermore, according to the United States Department of Agriculture’s Food Guide pyramid (61), this dose can be obtained from approximately 41 g, or about one-fourth cup of fresh betel leaves, which can perhaps easily be incorporated in daily diet. However, detailed pharmacokinetic investigations and pharmacodynamics analyses are necessary before conclusions on dose extrapolations, dietary incorporation, duration of consumption, etc., can be implemented.

**Conclusion**

Although the zeal and zest for discovering novel pharmaceutical leads from plant extracts have dwindled in recent years, the dominance of plants as superior sources of new drug discovery is unchallengeable. Exploiting the bounty of Mother Nature to identify and isolate valuable cancer-fighting agents from fruits, vegetables, and spices is a priority considering the increasing incidence of cancer in the world population. In particular, food materials labeled as "generally recognized as safe" (GRAS) are appealing sources to identify xenohormetic molecules that offer health-promoting effects and that complement the chemical space of drugs. No wonder the emergence of Foodinformatics, a new variant of Cheminformatics, will uncover potential applications of bioactive food chemicals using computational approaches.

*Piper betel*, an exotic condiment, reported to be a treasure of bioactive phenolics, possesses great potential to fight against cancers of oral, mammary, prostate, skin, and gastric origin. Much of these powers of betel leaf phytochemicals remain unharvested and call for extensive research to better understand their mechanism(s) of action and clearly demarcate their chemopreventive and chemotherapeutic roles. Through this review, we have attempted to summarize the advances in understanding the betel leaf action, its constituents, and their anti- and pro-oxidant nature, which bear chemopreventive and chemotherapeutic ramifications. We place into perspective the two seemingly intertwined preventive and therapeutic activities by discussing the physiologic difference in ROS levels in normal versus cancer cells and how this exposes an exploitable vulnerability of cancer cells, which can be appropriately “tuned” to enhance cancer cell selectivity to enable design of novel approaches for the management of this insidious disease.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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