# Recent Progress In Bioavailability and Synergy of Curcumin, Quercetin, and Resveratrol

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# Introduction

Dietary supplementation of curcumin and other polyphenols confer many beneficial health effects, including prevention and treatment of cancer, cardiovascular disease, and diverse other inflammatory conditions. Efforts have been made to increase their poor bioavailability in order to increase their efficacy and lower the necessary dose.

Numerous preclinical and clinical trials have recently been undertaken to investigate the bioavailability and bioefficacy of polyphenolic compounds.[1] Major gains have been made to our knowledge of polyphenol absorption and metabolism. Various modifications to free polyphenolics (encapsulation, addition of piperine, nanoparticles, phospholipid carriers) and combinations of polyphenolics have been evaluated for their effects on absorption and efficacy. The challenges of assessing bioavailability and the concept of synergistic interactions between polyphenolics will be introduced. The purpose of this review is to place Lund and Mantuso's recent study of curcumin, quercetin and resveratrol[2] in the context of others to illuminate the current state of knowledge and guide further inquiry.

# Bioavailability of polyphenolics

It is well recognized that polyphenolic compounds have relatively poor bioavailability. Lipinski's Rule of 5 states that compounds with five or more hydrogen bond donors (OH and NH groups), ten or more hydrogen bond acceptors (e.g. N and O), a molecular weight greater than 500, and Log P greater than 5 are usually poorly absorbed orally.[3, 4]

In order for a polyphenol to achieve an effect *in vitro,* concentration can range >1000-fold, from <0.1 uM/L to >100 uM/L. However, physiologic concentrations do not exceed 10 uM/L, so the effects of polyphenols *in vitro* at concentrations in excess of this are generally not clinically valid, with the possible exception of the intestinal lumen.[5]

Some experiments of polyphenol bioavailability have been carried out using the Caco-2 cell culture model.[6] Caco-2 human colon cancer cells have been widely used to predict

intestinal absorption of orally administered drugs and other compounds.[7] Although derived from colon carcinoma, the cells differentiate when cultured under certain conditions to structurally and functionally resemble the enterocytes lining the small intestine. The *in vitro* apparent permeability (P-app) across Caco-2 monolayers correlates reliably with the *in vivo* fraction absorbed.

It is known that polyphenols interact non-covalently with proteins in plasma through hydrophilic or hydrophobic bonds, thus affecting bioavailability.[8] Bioavailability of polyphenols is also significantly reduced by enzyme and microbial-mediated biotransformation and active efflux as well as by their physiochemical properties.[9] The majority of polyphenols are not subject to Phase I hepatic detoxification due to their unfavorable structure for cytochrome P450 metabolism. Instead they are subject to direct Phase II metabolism (glucuronidation, sulfation and methylation). Females are more efficient in the glucuronidation of resveratrol.[10] Polyphenols such as quercetin can modulate the intestinal microbiota and indirectly interfere with their own bioavailability.[11] Factors such as these are responsible for the unpredictable plasma levels of polyphenolic compounds seen following oral administration.

# Curcumin

The biotransformation and pharmacokinetics of curcumin will serve as an example here. Curcumin is the yellow pigment in turmeric (*Curcuma longa*), curry powder, and mustard. It has poor solubility when ingested, and most is excreted in the feces and only small amounts of curcumin or its metabolites appear in blood. When absorbed, curcumin is quickly reduced in the intestine and conjugated in the liver to several glucuronide and sulfate products.[12] In human studies, doses of curcumin up to 180 mg have produced no detectable plasma levels.[13] Doses up to 8 g have yielded only 0.5-2 uM.[14] Curcumin concentration of 10 nmol/g tissue in human colorectal mucosa have been obtained with oral consumption of up to 3.6 g curcumin.[15]

Doses of curcumin up to 12 g/day have been shown to be safe in Phase I clinical trials.[16] To achieve better bioavailability and reduce the dose of curcumin, various approaches have been taken. Piperine has been used as an adjuvant to inhibit glucuronidation. Liposomes, nanoparticles, phospholipid complexes, and structural analogues of curcumin (e.g., EF-24) have also been used to enhance absorption.[17] An excellent review was recently published of nanotechnologies to enhance delivery of curcumin, quercetin and resveratrol for their anticancer effects *in vitro* and in mice.[18]

# Quercetin

Quercetin is another example of a polyphenol with discrepancy observed between *in vitro* and *in vivo* studies attributed to absorption and metabolism. Quercetin (one of the most abundant natural flavonoids) is found at high concentrations in onions, apples, berries, red wine, broccoli, capers, pomegranate, and *Ginkgo biloba*. Although quercetin has been shown to possess effects including anti-inflammatory, antioxidant, anti-cancer, anti-anaphylaxis and anti-aging, it is unstable, has poor solubility and permeability, and low bioavailability Approaches used to improve bioavailability of quercetin include liposomes, nanoparticles, inclusion complexes, and micelles.[19]

# Resveratrol

Resveratrol, produced in berries, grapes, and peanuts in response to stress, injury, UV radiation and fungal infection,[20] is a third example of a polyphenolic compound with various beneficial effects. Resveratrol also is susceptibile to oxidative decomposition, has poor solubility and low bioavailability, in large part due to extensive phase II metabolism.[21] *In vitro* and animal studies have shown that resveratrol can act on a wide range of molecular targets, including sirtuins, influencing aging, transcription, apoptosis, inflammation, and stress resistance.[22] Organic anion transporting polypeptides have recently been found in hamster ovary and breast cells to function as cellular uptake transporters for resveratrol and its major sulfates, and account for bioactivity.[23]

The implication is clear that the proven biological effects of polyphenols *in vivo* do not correlate well with what we can observe about their bioavailability *in vitro.* This discrepancy has led to various strategies to improve their bioavailability and their bioactivity. Curcumin, quercetin and resveratrol will again serve as examples for how bioactivity can be improved.

# Formulation approaches for improving bioavailability of polyphenols

## *Piperine*

Piperine is the alkaloid responsible for the pungency of black pepper (*Piper nigrum)* and long pepper (*Piper longum).* Piperine strongly inhibits glucuronidation, affects the ultrastructure of intestinal brush border, and increases gastrointestinal transit time, thereby increasing absorption.[24, 25, 26] In human volunteers, concomitant administration of 20 mg piperine with 2 g curcumin increased serum concentration by 2000% in the following 15 – 60 minutes ($p < 0.01$ at 0.25 h and $p < 0.001$ at 1 h).[27] The complete mechanism of piperine's bioavailability enhancement is not known. It does inhibit human CYP3A4 and the efflux pump P-glycoprotein biotransforming reactions in the liver.[28]

A recent study demonstrated that piperine 20 mg alone and in combination with trans-resveratrol 200 mg significantly augmented cerebral blood flow (CBF) during task performance in comparison with placebo and resveratrol alone on separate days at least a week apart.[29] The plasma concentrations of resveratrol and its metabolites were not significantly different between the treatments, indicating that co-supplementation of piperine with resveratrol enhances the bioefficacy of resveratrol with regard to CBF effects, but not cognitive performance, and does this without altering bioavailability.

## *Lecithin, Phosphatidyl Choline, Proliposomes, Liposomes, and Phytosomes*

Another method for enhancing bioavailability is complexing curcumin with a phospholipid, known as a phytosome. The phosphatidylcholine-curcumin complex is more readily incorporated into lipophilic cell membranes, making it significantly more bioavailable than unbound curcumin. One 500 mg dose of this complex is composed of 100 mg curcuminoids (ratio curcumin : demethoxycurcumin : bis-demethoxycurcumin 33 : 8 : 1), 200 mg soy lecithin and 200 mg microcrystalline cellulose. A randomized double-blind crossover trial of the complex and a standardized curcuminoid mixture showed curcuminoid absorption (plasma level) was about 29-fold higher for the complex.[30] However, only phase-2 metabolites were detected. Demethoxycurcumin, a more potent analogue in many *in vitro* anti-inflammatory assays, was the major plasma curcuminoid after administration of the complex.

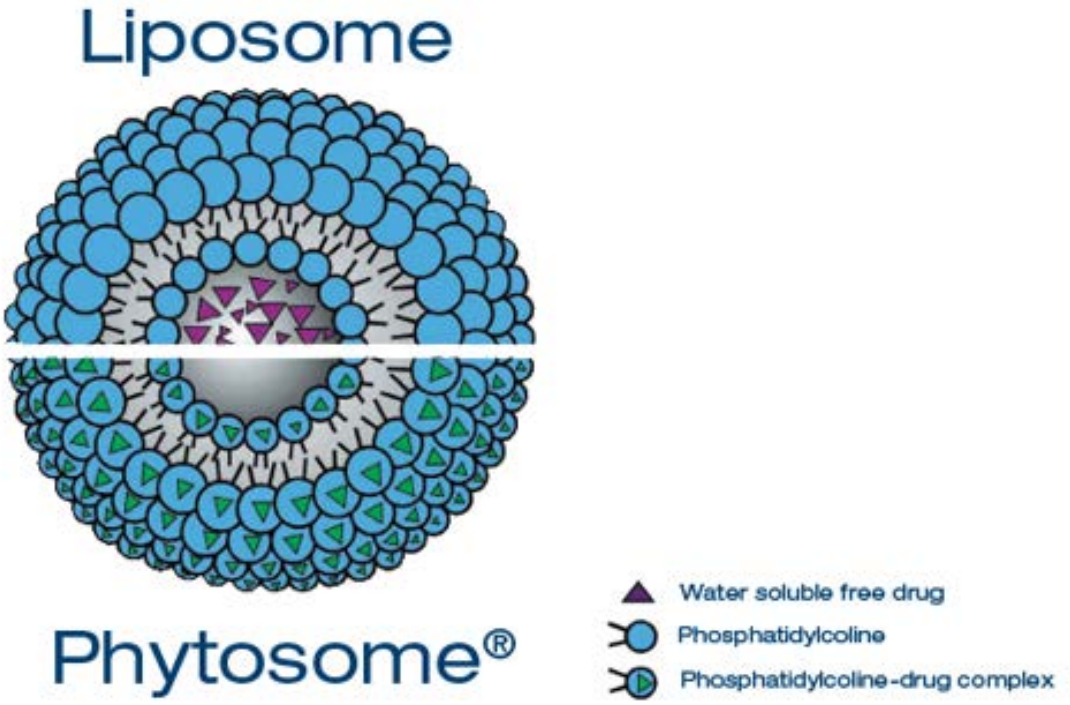


Fig. 1. Differences between a Phytosome® and a Liposome.

Although similar, phytosomes and liposomes have some basic differences (see Figure 1). The active ingredient in a liposome is dissolved in a central cavity, which limits its molecular interaction because of the surrounding phospholipid. In a phytosome, the active ingredient is dispersed in the phospholipid matrix (soy lecithin) and is integrated into the lipid membrane. Liposomes contain approximately five times the amount of phospholipids as phytosomes.[31]

Liposomes and phytosomes have been demonstrated to be excellent carriers for polyphenols, due to their biocompatibility, wide choice of physico-chemical properties and easy preparation.[32] Conversion of polyphenols into phytosomes improves efficacy without compromising safety. Phytosome technology creates bonds between individual polyphenol molecules and one or more molecules of the phospholipid, phosphatidylcholine (PC). Molecular imaging reveals that PC molecule(s) enwrap each polyphenol; upon oral intake the amphipathic PC molecules probably escort the polyphenol through the intestinal epithelial cell membrane, and then into the bloodstream.[33]

Aqueous solubility of quercetin improved by 12 fold (from 3.44 μg/ ml to 36.81 μg/ ml) in a quercetin-phospholipid complex, and bioactivity of quercetin was not adversely affected.[34]

Proliposomes are powdered mixtures of drug and lipid, intended to produce multi-lamellar liposomes upon contact with aqueous media entrapping adequately hydrophobic drugs.[35] Proliposomes have distinct advantages over liposomes, as the free flowing powder can be incorporated into solid dosage forms such as capsules or tablets. The simple process of preparation makes them more suitable for industrial scale manufacturing. Multi-lamellar liposomes containing drug molecules are believed to be absorbed *via* lymphatic absorption. Based on lipid composition and type of lipid, there are two possible ways for absorption of entrapped drug. First, intact liposomes may be absorbed *via* endocytosis by enterocytes. Second, due to their considerable size, the absorbed liposomes may be transported *via* the lymphatic system into systemic

circulation. Hence proliposomes can be a solution to issues related to solubility, permeability, P-glycoprotein efflux, and hepatic metabolism of polyphenols.[36]

A Chinese group developed a novel curcumin-phytosome-loaded chitosan microspheres (Cur-PS-CMs) delivery system and showed that the *in vitro* release rate of curcumin from it was slower than that from curcumin-loaded chitosan microspheres.[37] Rats dosed with Cur-PS-CMs had a 1.67- and a 1.07-fold enhancement of curcumin absorption compared with Cur-PS and Cur-CMs respectively. Half-life from Cur-PS-CMs (3.16h) was longer than that of Cur-PS (1.73h) and Cur-CMs (2.34h).

A proliposomal formulation of resveratrol resulted in significantly improved rate and extent of absorption of unmetabolized resveratrol *in vitro* and *in vivo*. Area under the curve and maximum concentration were twofold higher than plain resveratrol.[38]

## *Nanotechnology*

Nanoparticles (NPs) range from 1 to 100 nm in size and are composed of biodegradable and biocompatible polymers including starch, co-polylactic acid/glycolic acid (PLGA), and polylactic acid (PLA). NPs can be useful carriers for polyphenols in that they permit encapsulation of single or multiple compounds in their core or on their surface, and the time and rate of polymer degradation and subsequent delivery of the polyphenol can be controlled. Khushnud and Mousa recently reviewed studies published within the past 5 years on the use of NPs to enhance polyphenol delivery.[39]

Human serum albumin (HAS) NPs are non-toxic and immunogenic, and allow endothelial transcytosis of unbound and albumin-bound plasma constituents to the extravascular space. Mice with multiple melanomas were injected with both free and HSA encapsulated curcumin.[40] Nanoparticle-encapsulated curcumin concentrations were 14 times greater in melanomas compared to free curcumin. Xenograft mouse models were also used to test antitumor activity on human colon cancer (HCT116) and human pancreatic carcinoma (MiaPaCa2). Nanoparticle-bound curcumin inhibited tumor growth more (50%) for both cell lines compared to free curcumin (18%).

A Japanese group developed a curcumin formulation dispersed with colloidal nano-particles (Oblate) in 2011.[41] They found the AUC after oral administration to rats was greater than 40-fold higher than normal curcumin powder. Healthy human volunteers (8 males and 6 females) were then randomly assigned to 30 mg of the formulation or curcumin powder in 100 mL water. The AUC of the formulation was 27-fold higher than curcumin powder. They also found the 30 mg dose of the formulation in mineral water after alcohol ingestion significantly reduced acetaldehyde blood concentration versus mineral water only in a cross-over trial of 7 males. Acetaldehyde is considered to be responsible for the headache and other hangover symptoms associated with excessive alcohol drinking.

Conventional methods for the synthesis of biodegradable NPs rely on toxic molecules such as polyvinyl alcohol, polyethylene glycol, D-alpha-tocopheryl poly(ethylene glycol 1000) succinate as stabilizers/emulsifiers. A green approach uses plant extract synthesized PLA NPs for the sustained release of quercetin.[42]

A safe, self-nanoemulsifying lipid based delivery system of resveratrol has been shown to significantly increase *in vitro* cytotoxicity in MCF-7 breast cancer cells and increased anti-angiogenic activity *in vivo* in chick chorioallantoic membrane assays.[43] Resveratrol-loaded carboxymethyl chitosan NPs improve antioxidant activity *in vitro*, and in rats increase absorption and relative bioavailability by 3.516 times more than raw resveratrol.[44]

## Synergistic interactions of polyphenolics: more than the sum of its parts

The concept of synergy, that a whole or purified extract of a plant confers advantages over an isolated constituent, including the efficacy of low doses of herbs in an efficacious botanical formula, is a fundamental philosophical underpining of the major traditions of phytomedicine including Western herbalism, traditional Chinese medicine and Ayurveda. Evidence supporting synergism in herbal medicine has been reviewed by Williamson[45]

and Wagner and Ulrich-Merzenich.[46,47] Growing sophistication in analytical chemistry, and molecular, genomic, and biological methods has helped elucidate a variety of synergistic mechanisms of phytomedicines. Synergy is observed when constituents of an extract have multiple target mechanisms of action, and as we have seen above, are formulated to enhance bioavailabilty. The evolving rationale of synergy has led to greater legitimacy for phytotherapy.

Synergy is not always straightforward. A number of theoretical possibilities exist, that may or may not be seen in clinical practice, and may be unpredictable. It is possible that synergy can occur at one dose of a combination of substances and antagonism at another. Other potential complicating factors are the presence of unstable constituents, length of administration, microflora metabolism, host factors such as pH, and unknown active constituents.

A team of Dutch authors recently reviewed the mechanisms of combined action of chemopreventive dietary compounds.[48] These agents can show significant activity at concentrations where any single one agent is inactive, suggesting synergy. Although mechanistic understanding is limited, numerous combinations of complementary modes of action may be at play. Evidence is mounting that the activity of phytochemicals administered as dietary supplements alone do not explain observed health benefits of a diet rich in fruits, vegetables, spices, tea, coffee and wine.

## Comparative bioavailability and synergy of polyphenol formulations

Differences in study design, subjects, analytical methods, and administration significantly limit comparisons between different polyphenol formulations. Here we shall examine three studies that have made comparative measurements of different formulations of polyphenols.

The first study was a pilot cross-over design of 11 healthy volunteers that compared 2000 mg of a patented formulation, with equivalent doses of a combination of curcumin-

lecithin-piperine, and normal curcumin.[49] The formula content in blood measured by HPLC at 1, 2, 3, 4, 5, 6 and 8 h post-drug was 6.93-fold greater in the AUC than normal curcumin and 6.37-fold compared to the curcumin-lecithin-piperine formula.

The second study focused on comparative increases in relative absorption of curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin) and the metabolite tetra- hydrocurcumin after oral administration of three different curcumin formulations in comparison to a standardized curcumin mixture of 1,800 total curcumoids (CS).[50] The three formulations were equivalent doses (376 mg total curcuminoids) of a curcumin phytosome (CP), curcumin with volatile oils of turmeric rhizome (CTR), and a novel formulation of curcumin with a water soluble carrier (polyvinyl pyrrolidone) and tocopherol and ascorbyl palmitate as antioxidants) (CHC). 12 healthy volunteers completed this randomized, double-blind, crossover study, consisting of 4 trials with 9 blood draws each, separated by at least 7 days. Samples were analyzed by HPLC-MS/MS. Total curcuminoids appearance in the blood was 1.3-fold higher for CTR and 7.9-fold higher for CP in comparison to unformulated CS. CHC showed a 45.9-fold higher absorption over CS and significantly improved absorption over CP (5.8-fold) and CTR (34.9-fold, all $p < 0.001$).

The third study, a recent *in vitro* epithelial model of absorption of various combinations of quercetin (Q), resveratrol (R), and curcumin (C), provides preliminary evidence of the respective bioavailability of these three bioactive polyphenols across a caco-2 monolayer and how they can act synergistically.[2] The three polyphenols were quantified using an Alliance HPLC system (Waters Corporation, MA). The apparent permeability coefficient ($P_{app}$, cm/s) was calculated for each compound/combination using the following equation:

$P_{app}=( dC_b/dT)/(C_a \cdot A)$ where ($dC_b/dT$) is the rate of appearance of the constituent on the basal side (nmol/s), $C_a$ is the concentration of the constituent on the apical side (50 μM) and $A$ is the area of the monolayer (0.3 $cm^2$). The $P_{app}$, cm/s describes the ability of individual compounds to pass through the cell monolayer under the experimental

conditions.

The molecular structure of quercetin (Q), resveratrol (R) and curcumin (C) share similar characteristics that suggest they may have similar routes of uptake and efflux and thus may affect each other's absorption. The authors hypothesized that combinations of the three compounds, with and without piperine (P), 200 uM, would therefore affect their apical-to-basal absorption. Q, R and C were applied apically in isolation or in combination at 50 uM and measured in the basal chamber at 30 minutes.

Resveratrol had the largest enhancement in permeability when combined with Q (310%), and then with C (300%). The combination of Q & C increased the permeability of R by 323% (from 7.70+/- 1.10 to 25.09 +/-0.48). The combination of Q, C, and P increased permeability the most (350%; 27.22+/-0.89).

In isolation, Q had the highest permeability (10.99+/-0.77), R had 7.77 +/-1.10, and C had the poorest (0.99+/- 0.11).

Curcumin had 147% increased permeability when combined with Q, and 188% increased permeability when combine with Q & R. Addition of P resulted in the greatest increase: 229%.

Quercetin permeability was not significantly enhanced with any combination, but was maximal when combined with R: (11.90 +/- 0.52) and worst when combined with R, C and P (8.89+/-0.40).

Piperine appeared to enhance C and R and adversely affect Q permeability.

These results suggest that delivering these compounds in combination may improve the acute absorption of curcumin and resveratrol compared to supplementation with single polyphenol, reducing the need for higher doses and simplifying treatment with combination formulas.

The authors acknowledge that earlier investigations with longer exposures to polyphenols have shown changes in expression of UGT1A1, CYP3A4 and P-gp. [51] [52] Therefore, long term use of these combinations may further affect their absorption profiles.

Finally, it is important to consider that the caco-2 model is a valid model of absorption but not necessarily bioavailability. Also, the caco-2 cells used in different laboratories around the world have diverged significantly, which makes it difficult to compare results across labs.[53]

This study strongly calls for an *in vivo* study to assess whether the *in vitro* findings are similar. A crossover human trial measuring absorption of the 3 polyphenols separately and in combination should be performed.

## Bioavailability of parent compounds vs. select metabolites

The data on the bioavailability of polyphenols presented above considered the presence of intact polyphenols *in vitro* or in the blood, i.e. the ingested compounds or their conjugates. The trillions of intestinal microflora also play a significant role in the metabolism of polyphenols. After microbial enzyme-catalyzed deconjugation of any polyphenol conjugates that reach the colon, there are 2 possible routes available; (1) absorption of the intact polyphenol through the intestinal lining and passage into the bloodstream (as free or conjugated forms) or biotransformation of the original polyphenol into metabolites. The absorption data presented above include the contribution of the absorption of intact polyphenols in the colon but do not include the breakdown contribution. Microbial metabolism of polyphenols can break them down into simpler phenolic compounds that are common to many different polyphenols, some of which could have unique biological effects. For example, Lactobacillus plantarum IFPL935 has been shown to significantly increase the concentration of the catabolites of red wine polyphenols.[54] Some of these microbial-derived metabolites may be responsible for the effects attributed to resveratrol.

Health benefits associated with curcumin may depend on the amount of certain curcuminoids in the various available formulations. Further studies are needed to determine which curcuminoids are most potent and what doses are most effective for clinical applications.

# Conclusion

Curcumin is a well-studied down-regulator of the inhibitory kappa B alpha kinase, a key activator of nuclear-factor kappa B.[55] Blocking this central mediator makes curcumin therapeutically active in various inflammatory conditions including arthritis, cardiovascular disease, metabolic disease, neurodegeneration and tumorigenesis.

Curcumin may work synergistically and have improved bioavailability when combined with other polyphenolics and phytomedicines. For example, for cardiovascular applications, quercetin, resveratrol, piperine, hawthorn berry, coleus forskohlii root, and ginger root may be considered. For musculoskeletal pain and health, quercetin, devil's claw root, boswellia gum resin, piperine, ginger root, rosemary leaf, wild lettuce, Jamaican dogwood bark, feverfew leaf and flower would be options. For respiratory support, quercetin, stinging nettle leaf, feverfew leaf and flower, goldenseal root, piperine and ginger root are considerations.

Curcumin's diverse array of molecular targets affords it great potential as a therapeutic agent. There is intense interest in its therapeutic potential as evidenced by the number of ongoing phase II and III clinical trials. The primary obstacle to utilizing curcumin therapeutically has been its limited systemic bioavailability, but there are studies suggesting the various curcumin formulations may make it more effective and better absorbed. Results from completed clinical trials are encouraging and trials currently being conducted for both inflammatory conditions and cancer should clarify curcumin's value as a therapeutic agent and confirm some of the mechanisms responsible for its efficacy.

The human pharmacokinetic data on bioavailability of polyphenols are incomplete, which

limits clinical research and product development. The synergistic effects of polyphenolics should be further explored for additional beneficial and reliable outcomes in the prevention and treatment of inflammatory conditions, including cancer and cardiovascular disease.

# Author

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He currently serves on the Scientific Advisory Boards for Gaia Herbs, Inc., Kamedis, and Nordic Naturals.

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