Anti(angiogenic) food components: can be a major source of bias in the investigation of angiogenesis inhibitors

Reza Rastmanesh[1]^, Abdalla Bowirrat[2], Ashim Gupta[3]^, Elizabeth Gilley[4], Kenneth Blum[2,4,5,6]

[1]Department of Nutrition, The Nutrition Society, London, UK; [2]Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel; [3]Future Biologics, Lawrenceville, GA, USA; [4]Center for Sports, Exercise, Psychiatry, Western University Health Sciences, Pomona, CA, USA; [5]The Kenneth Blum Behavioral & Neurogenetic Institute, LLC., Austin, TX, USA; [6]Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

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Correspondence to: Ashim Gupta, MS, PhD, MBA, DABRM, FABRM. Future Biologics, 2505 Newpoint Pkwy, Lawrenceville, GA 30043, USA. Email: Ashim6786@gmail.com; Reza Rastmanesh, PhD. Department of Nutrition, The Nutrition Society, Boyd Orr House, 10 Cambridge Court, 210 Shepherds Bush Road, London W6 7NJ, UK. Email: r.rastmanesh@gmail.com; Kenneth Blum, PhD. Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel; Center for Sports, Exercise, Psychiatry, Western University Health Sciences, Pomona, CA, USA; The Kenneth Blum Behavioral & Neurogenetic Institute, LLC., 54 Rainey Street Suite 1208, Austin, TX 78701, USA; Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary. Email: drd2gene@gmail.com.

Background: Natural and diet-derived angiogenesis inhibitors/promotors are widely found in diets. These compounds can in several ways impact the results of oncological research of angiogenesis inhibitors.

Methods: We very briefly overview some of the most important examples to show how these compounds can create a bias in current research of cancer. Implications of this expert opinion cover similar angiogenesis-related diseases.

Results: Significant intra-individual differences in terms of dietary intake and differential effect of food processing techniques result in differential bioactivity and bioavailability of these compounds. There are only a handful of validated dietary questionnaire to quantify natural angiogenesis inhibitors/promotors. A corollary consequence is that participants in non-randomized clinical trials will have different baseline levels of serum/plasma/tissue/organ diet-derived angiogenesis inhibitors/promotors. This will lead to creation of clinical uncertainty and a hidden bias and consequently creation of translational efficiency bias, sampling efficiency, and waste of resources. We call for developing and validating a semi-quantitative food frequency questionnaire (FFQ) to gather data on these agents, specifically designed for oncological research because there is a clear gap in the literature of oncology.

Conclusions: This might facilitate the discovery of better prognostic, diagnostic, preventive measures, and therapeutic agents for the management of different cancers. Implications of this paper cover similar settings like ophthalmologic research.

Keywords: Angiogenesis inhibitors; anti(angiogenic) food components; bias; oncological research; ophthalmological research

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^ ORCID: Ashim Gupta, 0000-0003-1224-2755; Reza Rastmanesh, 0000-0002-6221-9062.

Introduction

The potential of angiogenesis inhibitors or angiogenesis modulating agents as therapy in a wide range of cancers such as ovarian cancer (1), metastatic thyroid cancer (2), metastatic colorectal cancer (3), metastatic kidney cancer (4), cervical cancer (5), stromal tumors (6) has increased dramatically over the past 20 years by newly emerged clinically available agents. To mention a few, a similar trend is seen for other angiogenesis-related diseases such as retinal neovascularization and corneal neovascularization (7-9). Most of the recently published articles benefit from notable sophisticated methodology (1,2,4,6-9). However, neither the published clinical trials nor the registered clinical trials have used—or at least reported using—a quantitative questionnaire in their design to measure and/or adjust for a hidden bias created by natural or food-derived anti(angiogenic) compounds.

It is of great importance to understand that there are multiple antiangiogenic dietary and natural agents which can confound the results of clinical trials of angiogenesis inhibitors in several ways. For instance, through antagonizing or agonizing the target receptor. We identify and address some gaps that have been theoretically or methodologically overlooked in the design of clinical trials of angiogenesis inhibitors which may affect conclusions obtained from systematic reviews as well. Reviewing the whole antiangiogenic food components is beyond the scope of this short paper. However, we will only mention some of them, and it is our hope that readers can extrapolate from these examples to formulate a possible plethora of other obvious conditions where this bias can confound different settings of oncological research.

Food component examples: oncological researchers be aware.

Highlight box

Key recommendations

- We caution the oncology and ophthalmology fields that ignoring baseline levels of natural angiogenesis inhibitors/promotors (either dietary intake or serum/plasma/tissue levels), will lead to unwanted spurious results.

What was recommended and what is new?

- Prior to this, there was no specific recommendation regarding the importance of these compounds in oncological and ophthalmological research.
- The novel finding is that there is a potential unwanted bias brought about by the food based diet-derived natural angiogenesis inhibitors/promotors. Ignoring this bias can result in artifact results and misinterpretation of conclusions.

What is the implication, and what should change now?

- Implications of this expert opinion cover similar angiogenesis-related eye diseases (such as age-related macular degeneration, retinal/macular neovascularization, different types of retinopathy, dry eye diseases), a wide range of cancers, hypertension and cardiovascular outcomes, just to mention a few. There is an urgent need for developing and validating a semi-quantitative food frequency questionnaire to gather data on natural angiogenesis inhibitors/promotors.

Methods

We extensively searched various medical databases for studies that reported the use of a validated dietary questionnaire to quantify natural angiogenesis inhibitors/promotors. Articles in English came from databases including Google Scholar, Web of Science, OT Search, CINAHL, Medline, PubMed, OT Direct, Pedro, SID, ProQuest, Up to Date, OVID Medline, and Cochrane. English keywords included "angiogenesis", "angiogenesis inhibitor", "angiogenesis promotor" "anti-angiogenesis", "anti-angiogenesis inhibitor", "anti-angiogenesis promotor", "natural angiogenetic", "natural anti-angiogenetic", "dietary angiogenetic", "dietary anti-angiogenetic" "questionnaire", "validated questionnaire", "bioactive foods", "bioactive food component", "ophthalmology", "oncology", "cancer", "tumor", "vascularization", and "neovascularization". The search was performed with no time limits. We obtained remarkable results which we share below our experience and lessons learned.

Plant lectins

Plant lectins, are a special group of carbohydrate-binding proteins/glycoproteins with powerful anticancer properties, that occur in natural sources and foods like lentil, soybean, kidney bean, pea, mushroom, peanut, and foods like wheat, corn, tomato, banana, rice, potato which are being genetically modify for mass production. The amount of dietary intake of lectins in humans is significant and more importantly there is a significant inter-individual differences in terms of dietary lectin intake (10,11). Vegetarian diets are much richer in lectins (12) and most importantly, different types of food processing techniques drastically change the level of digestibility and solubility of lectin and its bioactivity and bioavailability (11,13,14).

There are different types of lectins. Concanavalin A is a legume lectin, has gained a great deal of attention for its remarkable anti-tumor and anti-proliferative activities to a variety of cancer cells (15). Galectins, another type of plant lectins, are involved in a variety of biological functions such as angiogenesis, maternal-fetal immune tolerance, placental development, and trophoblast invasion, and are currently regarded as important mediators of successful embryo implantation during pregnancy (16). Galectins are also implicated in the occurrence and development of many autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and type 1 diabetes by regulating apoptosis, cell adhesion, and other mechanisms such as translocation to nucleus by carbohydrate-recognition independent manner (17). Two most widely expressed members of the galectin family, are galectin-1 and galectin-3 have showed remarkable therapeutic potential in autoimmune diseases (18) and glioblastoma (19).

Surprisingly, there are some types of lectins (such as collectin-11 which is a soluble C-type lectin) with completely opposite properties. For instance, it was recently shown that collectin-11 plays an important role in melanoma cell proliferation and tumor growth in mice model (20). Consequently, it was just reported that in endothelial cells dimerization of the C-type lectin-like receptor CD93 promotes its binding to multimerin-2 (21). These observations provide insight into the future design of new drugs able to hamper CD93 function in neovascular pathologies. The standard protocol in randomized controlled trials (RCTs) is to randomly assign the participants/patients to two (or more) groups, and then to standardize them in terms of age, gender distribution, and severity of a given medical situation disease based on the baseline outcomes of interest. In a number of RCTs, no significance has been reported in mean differences of micronutrient and macronutrient intake. But researchers fail to report mean intake of food-derived anti(angiogenic) compounds, and the food processing techniques used by the participants, which in turn affects bioactivity and bioavailability of these bioactive compounds. This means that even randomization alone may not be a way of attenuating this type of bias.

There are relevant references available for the reader which provide in-depth details and summaries of amounts of active lectins, in commonly consumed foods, like wheat and wheat-derived products (10,11,22). For a comprehensive updated review on plant lectins and their promising futuristic anti-tumor effect, see the work of Konozy and Osman (23).

Lectins can inhibit angiogenesis (24) and downregulate telomerase activity, which is found in most tumor types including colorectal, breast, prostate, ovarian carcinomas, etc. Telomerase activity is increased in pre-invasive lesions of the breast, like ductal carcinoma *in situ*. Research suggests telomerase activity is activated early in breast carcinogenesis (25). A study of gastric cancer patients found that sensitivity for gastric fluid telomerase expression was 80%, specificity 84%, positive predictive value 74%, and negative predictive value 88% (26). These findings are especially important because to date, no randomized clinical trials have controlled for, or considered such a major confounding factor.

In the assessment for breast cancer and many other cancers, telomerase positivity has been proposed as a biomarker (27). It has been suggested that the scrapings and frozen portions of the cervical tissue removed from patients with abnormal cervical smears, be tested for telomerase positivity, as a biomarker for preneoplastic cervical disease (28). The absence of expression of estrogen receptor beta (ERbeta) has an associated relationship with low levels of telomerase activity, in tissue samples from patients with breast cancer. Differentiation grade and telomerase activity have significant correlation (29).

Collectively, since there is an association between angiogenesis inhibitors and telomerase activity (30-32), and because of the fact that natural anti(angiogenic) compounds differentially interact with angiogenesis inhibitors and telomerase activity (33-46), the net result is that the accuracy, precision and diagnostic and therapeutic value of these biomarkers would be compromised in oncology research. Therefore, a non-balanced dietary intake of plant lectins in participants of clinical trials could create clinical uncertainty and subtle statistical bias in both experimental animal research and oncology clinical trials.

Capsaicin

Capsaicin is a newly recognized angiogenesis inhibitor. It is found in pungent fruits, especially in red pepper. It may have valuable potential in the development of new pharmaceuticals for treatment of angiogenesis-dependent human disease. It is a known inhibitor of vascular endothelial growth factor (VEGF)-induced p38 mitogen-activated protein kinase, p125(FAK), and AKT activation.

A cultivated version of red pepper, known as CH-19 Sweet has two major capsaicinoids. Capsiate, a capsaicin analogue, dihydroderivative dihydrocapsiate. Capsiate may have potential to help block pathologic angiogenesis and vascular permeability caused by VEGF (47). In a rodent study, chemically induced urinary bladder carcinogenesis was significantly reduced by intake of dietary capsaicin (48). The intake of dietary capsaicin prevents oral cancer development, perhaps through enhancement of apoptosis in humans and the inhibition of malignant cell proliferation (49).

In most published papers, capsaicin is considered a potential anti-tumor compound, and its anti-cancer properties are mainly attributed to induction of apoptosis and autophagy, anti-proliferation, anti-angiogenesis, and anti-metastasis. The pivotal point here is that its biological functions are greatly influenced by its concentration and the effective concentration in different malignant tumors differs significantly, highlighting the importance of quantifying and measuring its oral intake in clinical trials in study arms. Moreover, it would be pertinent to note capsaicin can affect the anti-cancer activity of radiation therapy or conventional chemotherapeutic drugs (50). It is worth reminding that progression of cancer is an intricate multistep process consisting of angiogenesis of the primary tumor, then its invasion into the surrounding stroma, and eventually its migration to distant organs to produce metastases.

Importantly, there is a significant difference in effect between low capsaicin consumption which offers protection for gastric cancers and the effect of high capsaicin intake (51). It is noteworthy, that there are significant inter-individual differences in terms of red pepper intake (52). Additionally, it seems parsimonious to consider the fact that capsaicin-containing foods negatively influence the swallowing response (53), which may influence the results of clinical trials investigating similar outcomes in for example, esophageal cancer. There are also individual differences in perception of bitterness (54), pain (55), and satiety (56) following intake of different amounts of capsaicin. This phenomenon may confound the interpretation of data collected from such studies in terms of efficacy, adverse effects, etc. In this regard, we the authors of this article emphasize the importance of additional clinical trials to address this issue in their study protocols and design.

Polyphenols

Polyphenols are regarded as naturally occurring micronutrients that are present in plant kingdom as necessary physiological bioactive compounds (57). These compounds comprise a wide family of molecules bearing one or more phenolic rings and are present in several food sources like vegetables, green tea, red fruit, wine, grapes, and coffee (58). Most polyphenols exhibit antioxidants (59) and anti-inflammatory properties (60). However, their anti-angiogenic properties have recently been a focus of attention in cancer research (61).

Polyphenols

Considering polyphenols, antiangiogenic properties of natural polyphenols from red wine and green tea has been well-established (62). Resveratrol, as a known polyphenol, is an angiogenesis inhibitor whose anti-cancer effect is proven in many types of cancer (63,64). Resveratrol has dual effects on the expression and secretion of angiogenic factors (63,65,66). This compound has strong anti-angiogenesis properties, but there are some medical circumstances, in which it may induce angiogenesis (63,66). A recent review article has hypothesized that the effects of resveratrol on different cell types may not only be dependent on its dosage/concentration but also on the chemical and physical conditions surrounding systemic cells (63,65). In a study of mice induced by VEGF and basic fibroblast growth factor, resveratrol significantly inhibited corneal neovascularization (67-69). Interested readers may consult related references by Sagar *et al.* (70).

To the best of our knowledge, there are no clinical trial on angiogenesis inhibitors designed to assess the magnitude of bias following short-term or prolonged natural consumption of these compounds in oncological and ophthalmological research, especially as it relates to cancerous tumors. In fact, this is true for tumor-promoting or tumor-preventing properties in both oncological and ophthalmological investigations. Moreover, the oncological and ophthalmological field should carefully, consider that there are large inter-individual differences in terms of these compounds. For instance, there are significant inter-individual differences for alcohol and wine consumption between countries (71). This is particularly known in both Islamic and non-Islamic countries, and this can additionally create another uncertainty in international comparative studies.

Flavonoids

Flavonoids are a class of polyphenols, which inhibit

angiogenesis (72). Hypericin, an active ingredient in the medical herb St. John's Wort, inhibits pathological retinal neovascularization in a mouse model (73). Considering the multi-pharmacological effects of flavonoids, and the vastly individualized dietary intake, these unmeasured anti-angiogenetic compounds of flavonoids, make it problematic to rely on potentially flawed data from some clinical studies with small sample size and low power.

Despite these caveats, there was at least one investigation revealing a successful experience utilizing a validated dietary questionnaire. Specifically, Rodrigues *et al.* evaluated the Phenol-Explorer Food Composition database to estimate the dietary resveratrol intake (71), However, we the authors, have no knowledge concerning published studies related to any experimental data indicating such a bias created by other natural anti(angiogenic) compounds in oncological research.

Omega-3-polyunsaturated fatty acids (PUFAs) and other vitamins

Omega-3-PUFAs and other vitamins, similar considerations apply to other natural angiogenesis inhibitors like omega-3-PUFAs (74) which has been shown to reduce pathological retinal angiogenesis (75), age-related macular degeneration (76), colon cancer (77), breast cancer (78), and neuroblastoma (79).

Vitamin A

For example, vitamin A modulates the structure and antiangiogenic functions of the retinal pigment epithelial layer partly by up-regulating the expression of the angiogenesis-related extracellular matrix protein, thrombospondin-1, and the antiangiogenic factor, pigment epithelium-derived factor (80). Vitamin D (calcitriol) is a potent inhibitor of prostate cancer (81) and retinal neovascularization and may be of benefit in the treatment of a variety of eye diseases with a neovascular component (82). Vitamin E analogues inhibit angiogenesis by selective induction of apoptosis in proliferating endothelial cells (83). Furthermore, antiangiogenic and anticancer properties of unsaturated vitamin E are well-established (84).

Lycopene

Lycopene supplementation in rats was shown to reduce the level of VEGF and attenuated the angiogenesis (85). One study found that lycopene supplementation inhibited angiogenesis in human umbilical vein endothelial cells and rat aortic rings (86). Another study found that lycopene inhibited experimental metastasis of human hepatoma SK-Hep-1 cells in athymic nude mice (85).

The main methodologic question here is "Why is development of a unified food composition database and semi-quantitative food frequency questionnaire for anti(angiogenic) food components important for cutting-edge research related to oncology and ophthalmology?". Food composition tables and databases (FCTs and FCDBs), sometimes referred to as FCTs, mainly centralize data and provide the nutrient and energy content of foods of a certain country or region (87). These databases are required in order to convert foods from food consumption data to nutrient intakes. These tools are essential for many activities related to dietetics and nutrition. Sources of data, food description, component identification, and the coverage of foods and components are the main factors which can affect the quality of FCTs and FCDBs. However, most of these databases are being criticized for not being up-to-date (87,88). Furthermore, most of the current FCTs which are used in different countries are limited, containing a limited range of mostly generic food and drink items. It has been recently proposed that to reflect the wide range of food products available to common consumers and to improve accuracy of dietary assessment, a larger country-specific electronic FCDBs need to be developed (89).

The major methodologic issue is that data on anti(angiogenic) food components is available in very few composition tables, for only a limited number of foods and mainly for raw products. Another issue is that these databases tend to ignore the effects of food processing techniques on the level of digestibility and solubility of these compounds.

FCDBs are critically important because they serve as a base to develop 24-hour food recalls, FFQ, and semi-quantitative FFQ. A brief description of these dietary tools seems prudent and may help oncological investigations in the future, especially as it relates to morphing unwanted bias involving angiogenesis inhibitors:

- A 24-hour food recall is a nutritional assessment method in which participants are asked to report all beverages and foods that they consumed in the last 24 hours. This method relies on the individual to successfully recall the food/drink they have consumed in the preceding 24-hour period, and obviously provides only a single-day snapshot of their diet (90).

- A FFQ is a limited checklist of foods and beverages with a frequency response section for subjects to report how often each item was consumed over a specified period of time (91,92).
- Semi-quantitative FFQs collect portion size information as standardized portions or as a choice of portion sizes (91,92).

A careful appraisal of the methodology of most oncologic and ophthalmologic investigations show that, at best, participants are asked to refrain from alcohol and caffeine intake and severe physical activity prior (days) the initiation of a clinical trial. Surprisingly, there is ample literature on significant differences between enrolled participants in RCTs whose baseline dietary or serum/plasma levels of anti(angiogenic) food components were high even at baseline (93-95). Clearly, it would be most beneficial and more precise to measure baseline dietary intake of such bioactive compounds to attenuate our proposed bias. Furthermore, reportedly, based on the table of characteristics of the participants and dietary intake of the participants, it can be seen that in some RCTs the serum/plasma or organ/tissue levels anti(angiogenic) food components are significantly different between the intervention group and control group, even after randomization. For instance, consider a clinical trial that aims to investigate the effects of lycopene supplementation in two groups of cancer patients (i.e., the intervention group who will be supplemented with the lycopene and a control group who will be given a placebo). When serum lycopene levels between the two groups are significantly different at baseline, even when the participants were randomly assigned to two arms, how can the researchers rely on the statistical comparisons?

More importantly, there are dose-dependent relations between the agent being tested and primary/secondary outcomes, i.e., agents/drugs need to reach or exceed a defined threshold to show their effect. A further complication is that some bioactive agents like lycopene have an interaction with lipoproteins as carriers. Therefore, if the baseline dietary (or serum/plasma/tissue/organ) or levels of anti(angiogenic) food components are significantly different at baseline between arms, any results would be either biased or confounded even in the face of statistical adjustments.

Another critique is that there are ample supplemental studies on supplementation of bioactive compounds in cancer patients. For example, supplementation with curcumin (96) or lycopene (97). We herein point out that methodologically, the pre-requisite for such designs is to measure and report baseline dietary intake of these compounds (for instance curcumin or lycopene, respectively). With regard to both supplements (96,97) the researchers have failed to report baseline curcumin or lycopene intake, possibly due to the lack of any validated questionnaire utilized in their respective studies. We therefore caution the oncology and ophthalmology fields that without reporting baseline levels (either dietary intake or serum/plasma/tissue levels) will lead to unwanted spurious results.

Cross-over designs are considered common standard designs in many applications in some fields of science, however in the current case presented herein we believe cross-over designs are inappropriate. In our opinion, this bold statement is based on a number of caveats:

- Seasonal variation influencing intake of bioactive compounds (98,99);
- Difficulties in determination of wash-out periods (100,101);
- Interplay between chrono-nutrition and bioactive compounds and anti(angiogenic) food components [biological rhythms impact the activity of anti(angiogenic) food components bioactive compounds, that could impact both intake amounts and even biological activity of these compounds] (102).

We have developed a schematic to assist the readership in framing a better comprehension of our salient points (see *Figure 1*).

Conclusions

There are significant intra-individual differences in terms of dietary intake of natural angiogenesis inhibitors/promotors (e.g., some diets such as vegetarian diets contain higher amounts of these compounds), and most importantly, different types of food processing techniques drastically change the level of digestibility and solubility of these compounds and their bioactivity and bioavailability. On the other hand, biological functions of these compounds are greatly influenced by their concentration and the effective concentration in different malignant tumors differs significantly, which is in turn a function of their oral intake and food processing techniques, which obviously varies among different people and communities. There is no clinical trial on angiogenesis inhibitors designed to assess the magnitude of bias following short-term or prolonged natural consumption of these compounds in oncological and

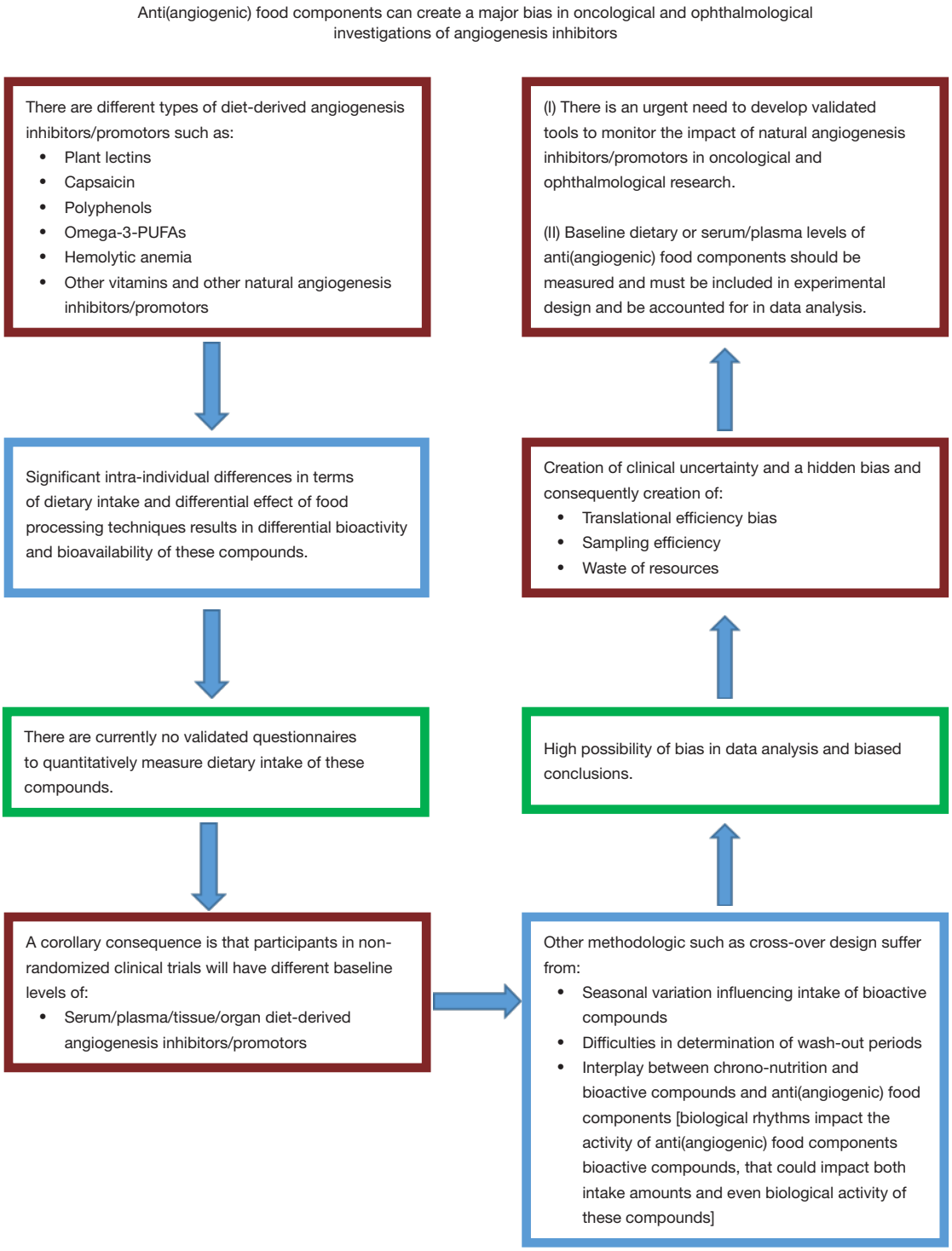

Figure 1 A simplified diagram of mechanisms by which different types of anti(angiogenic) food components may create a bias in studies of angiogenesis inhibitors. PUFAs, polyunsaturated fatty acids.

ophthalmological research, highlighting the importance of quantifying, and measuring the oral intake and their serum concentration in clinical trials and balancing the study arms based on baseline serum concertation of these compounds. The take home message herein is to inform the oncological and ophthalmological researchers of the potential unwanted bias of food-based diet-derived natural angiogenesis inhibitors/promotors as discussed. It is our hypothesis that these diet-derived natural angiogenesis inhibitors/promotors create a major bias in experimental research and clinical trials that aim to evaluate efficiency of angiogenesis inhibitors, particularly in oncological and ophthalmological diseases. Finally, our "out of the box" thinking may generate real interest and provide a new awakening for developing and validating a semi-quantitative FFQ to gather data on these agents, specifically designed for oncological research to assist in attenuating this problematic bias as espoused herein.

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Footnote

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