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Letter to the Editor

"How similar is similar enough? A sufficient similarity case study with *Ginkgo biloba* extract" by Catlin et al.; *Food and Chemical Toxicology* 118 (2018) 328–339

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Similarity of complex mixtures is a crucial topic in the context of research on herbal food supplements and medicines and especially with regards to toxicological assessments.

Recently, **Food and Chemical Toxicology** published two important papers on this topic both from the National Toxicology Program, USA and collaborators (Shipkowski et al 2018 and Catlin et al. 2018). Catlin et al. (2018) focuses on ‘similarity between different products and, therefore, is highly relevant for health products containing herbal substances or botanical preparations and potentially an important contribution to the safety of food supplements. It is certainly important to highlight that ‘Botanical dietary supplements with similar labels can vary widely in content’ (Catlin et al 2018) and this is in fact very well known. Importantly, as highlighted by Shipkowski et al. (2018) the purity of the material under toxicological evaluation is essential, including for example the levels of pesticides in the preparations (p. 965), which may impact strongly on any toxicological or pharmacological testing. This however is not incorporated into the strategy of research used by Catlin et al. (2018) and thus casts doubts on the applicability of the data from this study. Also one must ask, why are such products so variable and what is needed to assess this? In a recent study we demonstrated that out of the 35 samples of food supplements labelled as *Ginkgo biloba* which we analysed, 33 contain elevated levels of quercetin and /or rutin, or low levels of Ginkgo metabolites when compared with chemically well characterised the reference samples (Booker

1 et al 2016). The chemical variability of these generally unregulated commercial products
2 (food supplements) was huge. Their detection required a combination of analytical This leads
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4 to the key question: *Why are there these differences found on the markets?* This is the core
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6 point not addressed in the paper by Catlin et al (2018) and an important short-coming
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8 discussed in this commentary.
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11 In recent years a large body of analytical work has evolved focusing both on regulated and
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13 poorly or unregulated products and in order to understand the challenges posed by Catlin et al,
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15 such an understanding is essential. Poor extraction technique or deliberate adulteration along
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17 the value chain were identified as core problems by Booker and Heinrich (2016). Samples
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19 with disproportional levels of rutin or quercetin compared with other Gingko metabolites are
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21 likely to be adulterated with completely different species (especially Japanese temple tree -
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23 *Styphnolobium japonicum* (L.) Schott, syn: *Sophora japonicum* L.), either by accident or
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25 intentionally, and those samples with low or non-existent Gingko metabolite content may
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27 have been produced using poor extraction techniques (Booker et al 2016). Overall, these
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29 examples suggest either inadequate manufacturing conditions or deliberate adulterations.
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31 More broadly, this is linked to the regulatory status of herbal products with a medical use. For
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33 manufactured goods without a clearly defined regulatory status such as botanicals/food
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35 supplements. In many countries and regions, an established legal framework for herbal
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37 medicinal products exists. In the European Union the Traditional Herbal Regulation (THR -
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39 EU Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004)
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41 now defines a minimum standard which guarantees quality and safety of a herbal medical
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43 product sold with a medical claim for minor self-limiting diseases. Importantly, these are
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45 classed as registered medicines (Booker and Heinrich 2016). These are intended to treat or
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47 prevent diseases, or to restore, correct or modify physiological functions by pharmacological,
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49 immunological or metabolic action. Quality parameters are defined in a pharmacopoeia like
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51 the European Pharmacopoeia. In contrast, botanical food supplements are offered as food-like
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1 products that exert physiological or nutritional effects with the aim to supplement the normal
2 diet. Quality is assessed in essence based on the claims on the label. For this category of
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4 substances, no tight regulations are established in Europe and USA, where herbal dietary
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6 supplements do not need a formal approval before being marketed. Only if new ingredients
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8 are introduced or specific health effects are claimed, explicit regulations have to be observed
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10 in both regions (Abdel-Tawab, 2018; Koncic, 2018).
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14 The later point is relevant for food supplements containing comminuted *Ginkgo biloba* L.
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16 leaves or Ginkgo leaf extracts. Today both food supplements and fully regulated (registered
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18 and fully licensed) products are on the various markets globally. Unlike Ginkgo fruits, Ginkgo
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20 leaves have never been used as food. Beginning in the mid-1960, extracts from leaves of
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22 *Ginkgo biloba* were developed as pharmaceuticals by a German drug company for use in the
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24 treatment of peripheral and cerebral circulatory complaints as well as mental disorders. The
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26 development programme (Heinrich 2013) led to a patented manufacturing process providing a
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28 well characterized extract (EGb 761) with the aim to concentrate pharmacologically active
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30 substances (esp. terpene lactones) and removing problematic constituents (e.g. ginkgolic
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32 acids, 4-O-methylpyridoxine). Accordingly, EGb 761 is specified to contain 22.0 - 27.0 %
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34 Ginkgo flavone glycosides and 5.0 - 7.0 % terpene lactones (consisting of 2.8 - 3.4 %
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36 ginkgolides A, B, and C and 2.6 - 3.2 % bilobalide) and less than 5 ppm ginkgolic acids (Lang
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38 et al., 2013). There exists a well-developed body of clinical evidence for this type of an
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40 extract which is mainly positive, but results are inconsistent (Edwards et al 2015). Clearly
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42 from a consumers' perspective such a product will not be used because of a nutritional value,
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44 but because of the well documented pharmacological effects.
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53 Considerable evidence on the safety of a standardized Ginkgo leaf extract, EGb 761 is
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55 available and it has been concluded that if used together with synthetic drugs it 'appears to be
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57 safe 'as long as daily doses up to 240 mg are consumed' (Unger 2013). Ginkgo preparations
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59 may interact with anticoagulant, antiplatelet and NSAIDs medicines, increasing the risk of
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1 bleeding. Caution is advised when ginkgo is taken concomitantly with aminoglycosides or
2 ciclosporin, although this is only based on pre-clinical studies, and when in combination with
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4 anti-epileptics drugs (valproate, or valproate and phenytoin) as there have been case reports
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6 describing seizures in patients (causality not established). Therefore, Ginkgo's safety needs
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8 to be monitored – as is the case with other medications – and needs to be covered under
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12 pharmacovigilance (Williamson et al 2013, Edwards et al 2015).

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14 Although Ginkgo extracts have been developed specifically for medical use, food
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16 supplements are sold widely in many countries. While the regulatory hurdles of a drug
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18 authorization are bypassed by these means, these preparations are offered drug-like in form of
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21 tablets, capsules, oral solutions etc. and are promoted for their beneficial health effects with
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24 the help of ambiguous claims. Until now, the European Food Safety Authority has not
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26 approved any health claim for Ginkgo extracts or leaves due to the fact that no relationship
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28 between consumption of such supplements and beneficial physiological effects has been
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31 established (Czigle et al., 2018).

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34 If no health-promoting properties can be proven, one should at least expect that dietary
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36 supplements do not dispose of adverse effects. It ought to be obvious, that the safety and
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38 tolerability of herbal dietary supplement – when used as recommended - is within the
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40 responsibility of the manufacturer. This would imply that suppliers provide data to competent
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42 authorities, demonstrating that these basic requirements have been proven in accordance with
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44 commonly accepted scientific methods. In consequence, product-specific data should be
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46 available; raising the question of what research like the one by Catlin et al. (2018) can
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48 contribute. According to the US Dietary Supplement Health and Education Act,
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51 manufacturers are responsible for product safety and are requested to provide evidence for
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54 any proposed claim. However, in the case of an enacted product withdrawal, not the company
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57 needs to prove the safety of its product but the US Food and Drug Administration is required
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60 to demonstrate that the product is unsafe (Abdel-Tawab, 2018).

1 Specifications for *Ginkgo biloba* leaf extracts (GLE) – in contrast to many other herbal
2 ingredients of dietary supplements – have been laid down in numerous monographs (e.g. US
3 Pharmacopeia, European Pharmacopoeia, German Commission E, American Herbal
4 Pharmacopoeia, Health Canada, WHO). Therefore, an extract which complies with such
5 pharmacopoeial requirements should be at the focus of any testing for safety. As stated by
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7 Catlin et al (2018) in the US National Toxicology Program a *Ginkgo biloba* extract (NTP
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9 2013) was selected for case study development by the NTP. However, based on the NTP
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11 Technical Report 578 it does not comply with specifications as given in these monographs for
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13 medical and botanical products (i.e. it contained 31.2 % flavone glycosides, 15.4 % terpene
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15 lactones and 10.5 ppm ginkgolic acids), which, however, is not stated in the original report
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17 (NTP2013). This extract has not and still is not representative of the vast majority of the
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19 worldwide-marketed registered GLE-containing products. In the peer review of the NTP
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21 report this was stated explicitly by Dr. S. Dentali, representing the American Herbal
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23 Products Association: The extract ‘discussed in the draft Technical Report is not
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25 representative of other *Ginkgo biloba* leaf extracts marketed in the United States and is almost
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27 certainly not sold in the United States.’ (p. 15) Therefore, the extract studied by Catlin et al
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29 cannot be used for a safety assessment of commercial, chemically well characterized *G.*
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31 *biloba* products. One must ask why Catlin et al. (2018) tried at length to show similarity
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33 between products which one would expect to be dissimilar based on the existing regulatory
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35 framework and the justification for the use of such an untypical *Ginkgo* extract in the NTP is
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37 unclear. In addition one must query the methods used in their comparison, they are not
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39 accepted pharmacopoeial methods and will not detect possible adulterations or
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41 contaminations with potentially toxic constituents, poisonous plants, pesticides, heavy metals,
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43 mycotoxins etc.

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46 The study by Catlin et al. (2018) is still based on the assumption that a selected sample is
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48 representative for all products with the same label claim. However the limited phytochemical
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1 investigations and testing for a few selected biological effects makes this approach highly
2 problematic. As importantly, the description of methodological details in Catlin et al (2018) is
3 entirely insufficient and no experimental data are reported, making this study for all practical
4 purposes non-reproducible. This certainly contradicts the call by Shipkowski et al. for ‘best
5 practice’ (p. 969). The (in pharmacopoeial terms) non-validated analytical procedures used
6 clearly are not suitable for assessing the composition, possible adulterations and quality
7 standards of *Ginkgo biloba* products. For example, a combination product containing "another
8 'active' botanical (Gotu kola)" was found by all three applied methods to be similar to the
9 reference Ginkgo extract". Using the empirical equivalence testing model, even the highest
10 grade of similarity was determined for this product (sic).

11 Overall, this raises concerns about what conclusions can be drawn from this study. The
12 assessment of complex mixtures like herbal medical products / botanicals requires a detailed
13 understanding of the preparations’ composition. Otherwise, as it is the case in Catlin et al
14 (2018), the scientific validity of a study remains very limited. Composition and thus safety
15 must be understood in a regulatory context. The concerns identified here call for a better
16 understanding of the supply of herbal medicines (Booker and Heinrich 2016, and more
17 broadly for ‘a convergence of the diverse regulatory systems’ This would lead ,to an
18 adequate availability of herbal and traditional medicinal products to the patients without
19 neglecting public health’ (Wiesner & Knöss 2014).

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