Converting hydrophobic food ingredients possessing antitumor activity into amphiphilic excipient solubilizers.

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Editorial

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The molecules Tocopherol polyethylene glycol succinate (TPGS) (Figure 1) and polyoxyethylated castor oil (Figure 2) are amphiphiles and are used as solubilizers to enable aqueous solubility enhancement of hydrophobic molecules. Could the paradigm of succinylation followed by polyethoxylation be applied to food ingredients that present with inherent properties?

Food ingredients, such as the vanilloid capsaicin, which is the active constituent of chili peppers, the curcuminoid phenol, curcumin, the major constituent of the spice turmeric, and lignin, laricirecinol, which occurs in flaxseed and sesame seed, have been documented to possess antiproliferative and antitumorigenic properties. Capsaicin acts by blocking the degradation of IKBα, thereby preventing the translocation of the p65 subunit of NF-κB to the nucleus. It has also been reported to inhibit mitochondrial respiration by altering the permeability of the inner mitochondrial membrane. Curcumin acts on a host of pharmacological targets. It activates caspases and stimulates the release of cytochrome C, upregulates the proapoptotic factors BAX and AIF and downregulates the antiapoptotic factors Bcl-2 and Bcl-xL. It also inhibits growth factors such as EGF, VEGF and IGF-1. It has also been reported to inactivate HIF-1 via ARNT degradation. Lignans, such as

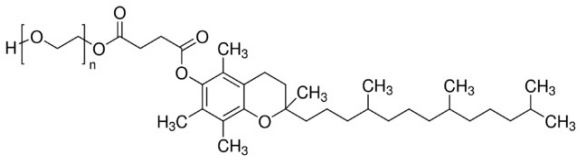

Figure 1 Tocopherol polyethylene glycol succinate (existing molecule)

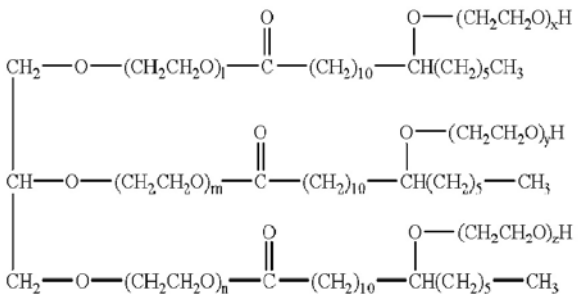

Figure 2 Polyoxyethylated castor oil (existing molecule)

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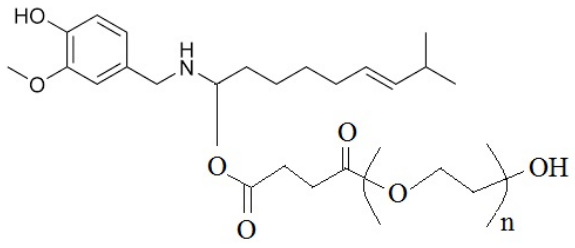

Figure 3 Capsaicin polyethylene glycol succinate (non-existent, un-synthesized, proposed molecule)

laricirecinol, inhibit estrogen induced angiogenic factors and downregulate VEGF. Flavonoids such as Quercetin have been reported to possess anticancer properties, probably due to the scavenging of reactive oxygen species (ROS).

The hydroxyl methoxy benzyl moiety present in the above food ingredients occurs as a recurrent motif in the structure of antitumorigenic compounds. This structure is an agonist for the vanilloid receptor which has recently been implicated in the modulation of apoptosis in actively proliferating cancer cells. It is therefore advantageous to succinylate (and subsequently polyoxyethylate) these compounds at a structural location other than the hydroxyl methoxy benzyl motifs (Figures 3, 4 and 5) so as to maximize the probability of retaining their antitumor activity. It appears that such a modification, i.e., monoesterification at selected hydroxyls is possible as has been demonstrated by the enzymatic regioselective monoesterification of flavonoids such as naringin and flavonin. The ketone group in capsaicin (Figure 3) is assumed to be capable of reduction to a hydroxyl before subsequent esterification and polyethoxylation. In summary, synthesizing the structures presented in Figures 3-5 does not seem to be an unsurmountable proposition.

Converting these hydrophobic food ingredients into amphiphilic compounds creates an opportunity whereby these amphiphiles can be used as 'excipient solubilizers' for increasing the solubility of APIs with a prominent mechanism of action (such as tyrosine kinase inhibitors), whilst themselves retaining their anticancer properties.

This approach is advantageous for several reasons. Extensive toxicological studies need not be performed on these 'excipients' because they are not professed to be active pharmaceutical ingredient(s) in the formulation. The regulatory burden is consequently decreased significantly. Assuming that these excipient molecules retain their 'pre-amphiphilic' anticancer properties to a significant extent, the probability of such formulations meeting clinical survival endpoints becomes logically more likely when compared to 'current best in class' API formulations.

They can be formulated with hydrophobic APIs regardless of the API mechanism(s) of action because these excipient solubilizers, for the most part, act on multiple pharmacological cancer signaling pathways making them 'generic' in effect, regardless of the tumor genesis, type or location in the body. In fact, the solubilizers can be chosen so that their mechanism(s) of action complement those of the API, thereby theoretically improving the

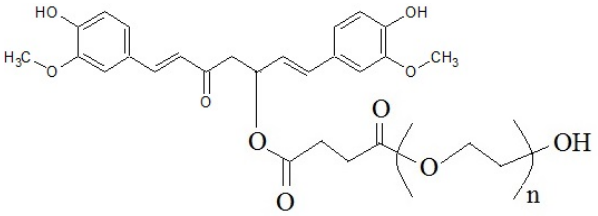

Figure 4 Curcumin polyethylene glycol succinate (non-existent, un-synthesized, proposed molecule)

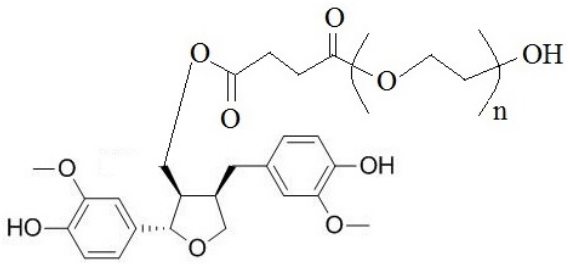

Figure 5 Laricirecinol polyethylene glycol succinate (non-existent, un-synthesized, proposed molecule)

clinical efficacy.

It may turn out that these solubilizers acquire additional antitumor mechanisms, or biological modifier mechanisms of action, that originate by dint of their amphiphilic nature. By all accounts, polyoxyetylated castor oil was not specifically selected as a solubilizer because it possessed efflux pump inhibitor activity. This activity was discovered later and fortuitously found to enhance the effect of the API. On the other hand, excipient molecule solubilizers that I suggest be synthesized/created, are already known to be potent antitumor agents in their 'non-amphiphilic' state. If, by virtue of their acquiring amphiphilic properties, they turn out to be MDR inhibitors as well, so much the better.

The paradigm of converting food ingredients with biological activity into excipients by 'amphiphilization' may even be extended to converting APIs into excipient solubilizers. As an example, there appears no *a priori* reason why the podophyllotoxin skeleton, the starting lead for a number of extremely efficacious cytotoxic agents such as etoposide and teniposide cannot be esterified and polyoxyethylated so to allow the resultant molecules to function as amphiphilic solubilizing excipients.

Scientists have retrospectively discovered that currently used excipient solubilizers such as TPGS and polyoxyethylated castor oil derivatives possess biological activity that enhances the API effect. Why not take a more proactive approach and deliberately design such excipient molecules and/or solubilizers?