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Food strategy: Antioxidants Synergistic effect of natural plant extracts

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ABSTRACT
This study is based on the exploitation of plant extracts and the subsequent conversion of knowledge into a tactile application in the food industry in order to promote sustainable solutions to various challenges, in particular the excessive use of synthetic products (food, food supplements, cosmetics, etc.). The latter has long been linked to many questions in terms of risks to human health (cancer diseases among others). While creating positive synergies with the various sectors (pharmaceutical, food, cosmetics, etc.) and the discovery of new paths (nutraceuticals, etc.), energy and cost aspects are of interest. Economical, effective, and natural are three basic valleys of research and applications, products or even molecules with antioxidant effects and their combinations in order to preserve the food system in particular and other sectors and integrate biodiversity into value chains.

1. Introduction:

The worldwide demand lately strives to return to natural and safer composition in order to shift to healthy diets that include sustainability considerations. Healthy diets that are sustainable and inclusive can be provided through food systems. This latest becoming a powerful driving force towards ending hunger, food insecurity, and malnutrition in all its forms **[1]**.

Conscious nutrition is a movement that has been seen as a challenge for food ingredient producers and suppliers **[2]**, especially over the last few decades, due to COVID-19 pandemic concerns **[1]** and other elevated diseases such as cancer with an estimated number of new invasive cancer cases 5370 each day in 2023 in the united states only **[3]**.

In the food industry, Antioxidants are mainly used to help preserve food and improve its shelf life by reducing free radicals, as well as to add flavor, color, and texture. Antioxidants can also be added to food to reduce the risk of disease and improve health **[4]**.

Free radicals are molecules that can cause oxidative stress and lead to damage to cells and organs **[4]**. High-fat content food systems (Lipids, meats, fish…) are the principal target of oxidative reactions. The primary factors affecting lipid oxidation are oxygen and temperature **[5]**. This deterioration in saturated and unsaturated fatty acids affects the organoleptic quality (off-odors, off-flavors, color, and textural changes) **[5]**, nutritional quality **[5]**, and consumer's safety of both natural and manufactured foods **[6-7]**.

Thus, food oxidation can cause to throwaway of food and this is a major global problem, as food waste contributes to climate change, depletes fertilizer, chemicals, energy, fuel, water, and land resources, and increases poverty and social equities. Mouat *et al*. (2022) **[8]** reported that by 2050, global food demand is estimated to increase between 70% and 110%.

These antioxidants play a crucial role in the food industry, and they are divided into natural and synthetic. Synthetic antioxidants are commonly used in processed foods and beverages and can also be found in cosmetics and other personal

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care products. They have been widely used thanks to their chemical stability and low cost **[9]**. While synthetic antioxidants are generally considered to be safe, some studies have linked them to potential health concerns **[6]**. For example, Xu *et al.* (2021) **[9]** reports that synthetic phenolic antioxidants butylated hydroxyanisole (BHA)(E320), butylated hydroxytoluene (BHT)(E321), and tertbutyl hydroquinone (TBHQ)(E319) engender carcinogenicity, cytotoxicity, oxidative stress induction, and endocrine-disrupting effects in excessive addition or incorrect use.

While ingredients sourced from natural resources and exhibit an antioxidant activity are considered natural antioxidants.

Aromatic and medicinal plant extracts are widely studied for their compositions, method of extraction, characterization, and other functionalities as potential in food preservation **[10]**. They have been reported as a source of antioxidants such as tocopherols, carotenoids, lignan compounds, flavonoids, polyphenols, and phenolic acids **[10]**. Their application reveals to be a necessity to replace the synthetic antioxidants mainly BHA, BHT, and TBHQ in many food matrices, since they are recognized as natural ingredients when compared to chemical antioxidants **[11-13]**.

A variety of therapeutic and pharmacological properties are affiliated with natural antioxidants **[7]**. Puertollano *et al.* (2011) **[4]** reports that natural antioxidants and polyphenols, including flavonoids, can retard the occurrence of various major health problems including cancer, and atherosclerosis… and maintain the body's antioxidant defense systems.

However, the antioxidant properties of whole plant extracts may be difficult to replicate and not sufficient to meet the needs of the food industry, due to the natural variability concerning the antioxidant contents and to difficulties in extraction and poor stability. In light of these problematic, it is essential to standardize formulations of natural compounds.

On the other hand, without standardized formulations, the natural antioxidants level required to occur preservation safety, may demonstrate a prooxidants effect **[14]**, be prohibitively expensive, or exceed levels permitted by regulatory and legislative. Even so, to the best of the authors' knowledge, rosemary extract is the only natural antioxidant included in the European list of food additives with the number E329 **[15]**.

As consequence, numerous researches strive into reducing the dosage of natural antioxidants with the help of synergistic effects while combining one or more plant extracts with antioxidant properties to provide an effective action. That may include the use of plants extracts and commercial antioxidant blends, Co-incorporation (micelles, liposomes, archaesomes, nano cochleates, and other nano delivery technics…), and simultaneous extraction of a mixture of different plant species "co-extraction". Reduction of dosage while obtaining the desired preservation safety is required for commercial reasons as well and thus is particularly important in food application. Furthermore, exploring a wide range of natural antioxidants and visualizing their mixture may prevent excessive usage of certain natural resources, have broad-based benefits for society, and decrease side effects.

This article has been prepared to consolidate research findings on natural antioxidants, their combinations, and synergism effects in food systems and discuss the future scope of the findings.

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2. Oxidations:

2.1. Oxidation in lipids:

The oxidation process in lipidic matrices is a very active research field **[16]** and comprises three phases: initiation, propagation, and termination. In the first phase, starting with an unsaturated fatty acid, losses of hydrogen atoms occur in the methylene-interrupted carbon of the isolated diene. Fatty acids that contain more double bonds have more methylation-interrupted carbon reaction sites, which doubles the rate of oxidation **[7]**. Heat, light, oxygen availability, unsaturated fatty acids composition, photosensitizers, heavy metals, enzymes, metalloproteins, and metal ions (Fe^{2+} and Cu^{2+}) **[10]** act as initiators and catalysts and thereby the production of lipid radicals. The presence of ground-state oxygen cannot initiate fatty acid oxidation without the oxidation favorable conditions **[17]**. The energy of the generated alkyl radical is reduced by isomerization to form conjugated diene **[5]**. Propagation is when the formed alkyl radical associates with atmospheric oxygen (O_2) and form a peroxyl radical ($ROO^{\cdot}$). This peroxyl radical can react with another lipid molecule (RH) to produce a new lipid radical ($R^{\cdot}$) and a hydroperoxide molecule (ROOH). The newly formed lipid radical can then react with another oxygen molecule, and the process continues, leading to the propagation of the chain reaction. Which turn in results the production of primary lipid peroxidation products (ROOH), that are not volatiles with no rancid aromas. In addition, in the presence of heat, light, or transition metals, reduction of ROOH occurs, to produce an alkoxyl radical ($RO^{\cdot}$) and a hydroxyl radical ($^{\cdot}$ OH). Alkoxyl radical ($RO^{\cdot}$), hydroxyl radical ($^{\cdot}$ OH), superoxide anion radical (O_2^{*-}), singlet oxygen (O_2), and peroxyl lipid radical (ROO*) are a reactive oxygen species (ROS) that can attack the aliphatic chain of the fatty acids. And generating secondary lipid peroxidation products such as aldehydes, hexane, ketones, and malonaldehyde, characteristics of rancid aromas, and undesirable modifications in food. In the termination phase, the free radicals react in various combinations and generate a radical-free molecule such as fatty acid polymers that precipitate and increase the viscosity of the product. Other unstable products are also generated which also affect the quality of the products. In this phase, no action is meaningful, since organoleptic and nutritional quality are already degraded, and every action made at this point is

considered to be food fraud. Lastly, these radical reactions can better describe the side reactions of lipid oxidation and provide new directions for lipid oxidation studies.

2.2. Oxidation in proteins:

Protein oxidation is the second most abundant cause of food spoilage. The composition of meat has a substantial influence on its oxidative stability. Oxidation of proteins exhibited in the amino acid side chains and protein chain. As for lipid oxidation, the presence of reactive oxygen species (ROS), myoglobin, metal catalysts, and non-radical species such as H_2O_2, influence the physicochemical reactions between proteins. The oxidation products of proteins oxidation are carbonyls, hydroperoxides, and sulfoxides. Protein oxidation promotes fragmentation by the scission of peptide linkages and protein aggregation which leads to reduce the protein solubility **[7]**. Thus, vary widely in the chemical structure of meat products affects their juiciness', tenderness, color, loss of protein digestibility, and nutritional quality. Nowadays, the poultry sector, one of the major domains in meat production, is pressed to improve mass production, which means fast growth rates and large breast muscles. As consequence, birds turn to be vulnerable to oxidation damage in tissues, which turns in results serious health problems, low meat quality, missed poultry performance, and loss of resources **[18]**.

2.3. Oxidation in emulsion:

Oxidation in oil-water emulsions is a common problem that can cause a variety of negative effects. On the other hand, it occurs rapidly compared to edible oil oxidation. The localization of antioxidants in emulsions, micelles, and liposomes may be determinators factors of the antioxidant's capability. Oil-water emulsion oxidation promoted by the metal ion is very likely since the water-oil interface increases the contact between the oil phase and prooxidant metals. Schroën et *al.* (2022) **[16]** reported that in oil/water emulsions, the initiation phase is co-determined by the initial ("pre-existing") hydroperoxide concentration radical. Also, the charge of molecular surfactant plays an important role in oxidative stability. Bayram & Decker (2023) **[19]** mentioned that using positively charged surfactants as cationic surfactants, carbohydrates, and proteins can prevent contact between the oil phase and prooxidants metals due to a repulse toward positively charged metal ions. The opposite is true, where using a negatively charged surfactant attracts the metal ions and therefore increases oxidation.
In an oil-water emulsion, oil is dispersed into microparticles. Every particle is surrounded by an interface and water. Hopia et *al.* (1996) **[20]** shows that tocopherol is better than carnosic acid and carnosol in the context of preventing oxidation and hexanal formation in the oil-water emulsion. Carnosic acid is relatively less lipophilic than tocopherol, this final is fixed in lipid particles and therefore prevents lipid oxidation better than the relatively hydrophilic, which is partitioned in the water-oil interface and water. Hydrophilic and hydrophobic antioxidants do have not the same antioxidant efficiency in bulk oil or oil-water emulsions. The antioxidants paradox or polar paradox refers to a phenomenon where hydrophilic antioxidants are more efficient than hydrophobic in edible oils. On the other hand, using the polar paradox in predicting the antioxidant activity does not apply to modified antioxidants. where the antioxidants are modified with different alkyl chain lengths to modify their solubility. Huang *et al.* (1996) **[21]** shows the antioxidant activity of Methyl carnosate, a modified carnosic acid in bulk oil and oil-water emulsions. As mentioned before, the paradox theory is not applicable since methyl carnosate exhibit high antioxidant activity compared to carnosic acid in oil and in the emulsion system. Hait-Darshan *et al.* (2009) **[22]** examined the antioxidants synergism effect between spinach-derived natural antioxidants and three commercial antioxidants: Caffeic acid, ferulic acid, and epigallocatechin-3-gallate (EGCG) in the phosphatidylcholine liposome system. Hydrophilic antioxidants such as EGCG and Caffeic acid appears to increase the antioxidant activity of spinach-derived natural extract more than ferulic acid. This is related to the differences in hydro-solubility of the three chosen antioxidants, therefore the partition coefficient at the aqueous phase. The antioxidant paradox is implicated in this example since, despite the fact that ferulic acid is relatively hydrophobic, which was expected to enhance the antioxidant activity of the hydrophilic spinach natural antioxidants, ferulic acid failed to do. These findings demonstrate the importance of using antioxidant combinations. In most studies of antioxidant activity, oxidation has been seen as one single response. However, food oxidation is a complex multistep process, it is important to study the ability of natural antioxidants to inhibit the various steps of the oxidation process.

3. Mechanism action of natural antioxidants:

Antioxidants are substances that can inhibit or prevent the harmful effects of reactive oxygen species (ROS), such as free radicals, by either neutralizing them or repairing the damage they cause to cells and tissues. The mechanism involved in the antioxidant activity of natural antioxidants is dependent on molecular structure.

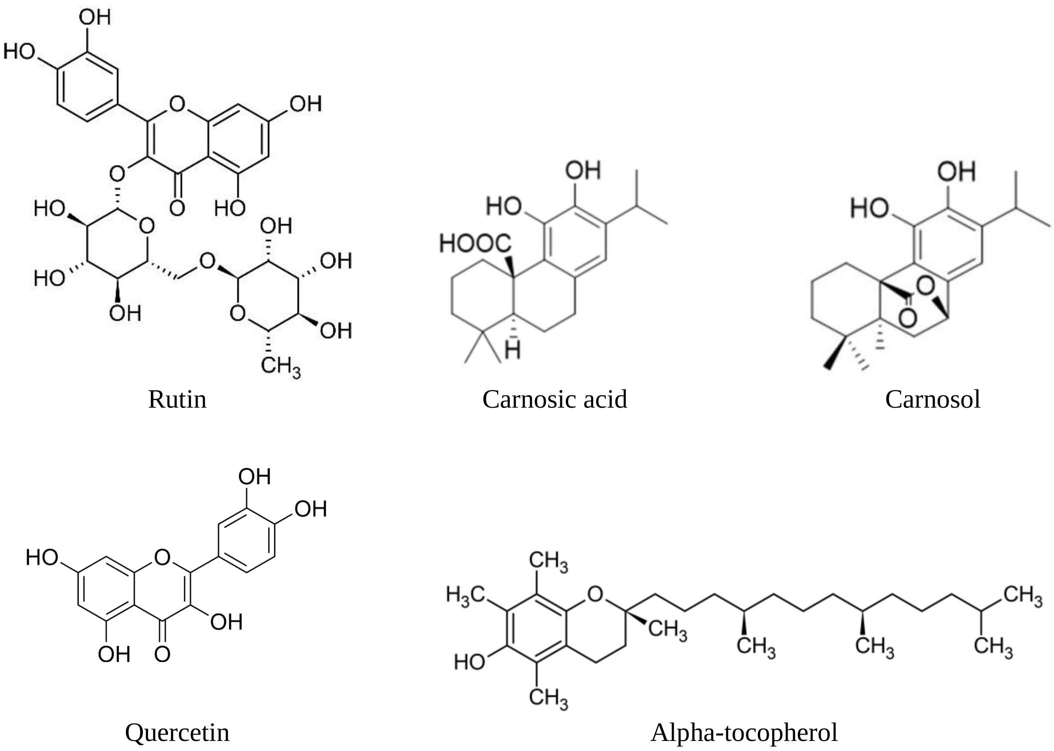

Figure 1. Molecular structure of natural antioxidant.

3.1. Primary chain breaking:

The phenolics present in the natural antioxidants with low redox potentials can thermodynamically donate hydrogen and thereby break the radical chain by reducing radicals. which turns in results slowing down the initiation and propagation phases of lipid oxidation.

$$LOO^{\cdot} + AH \rightarrow LOOH + A^{\cdot} \qquad (1)$$

During storage, scavenger free radicals are depleted due to the donation of hydrogen, therefore they lose their antioxidant ability as preservatives. Both carnosic acid and carnosol, two phenolic acids work as primary chain-breaking antioxidants. Birtić *et al.* (2015) **[23]** has been reported that the radical chain-breaking action is caused by the presence of the two O-phenolic hydroxyl groups in C11 and C12. Pires *et al.* (2017) **[12]** reported that rosemary extracts containing 4.4% of phenolic diterpenes at 480mg/kg in chicken burgers exhibit a high antioxidant efficiency compared to an equivalent amount of active ingredient of BHA 20mg/kg. the results promote the replacement of BHA with rosemary extract. Similarly, Tocopherol is a well-known compound widely commercialized that can interrupt lipid autoxidation by interfering with either the chain propagation or the decomposition products. Tocopherols and related compounds are found in vegetable oils at a level of 50-1000mg/kg, in animal fats at levels of 20-50 mg/kg, and in cereal germ oil can exceed levels of 1500-5000mg/kg **[24]**.

3.2. Metal chelating:

The metal chelating mechanism is when high valency trace metals such as iron, and copper… induce oxidation and the context is preventing the complexation of metals with lipids. The advantage of antioxidants with a metal chelating mechanism (AH) is stabilizing the Metal and blocking the initiation phase of the oxidation process. And in turn, a small number of antioxidants will be utilized, since transition metals are only in trace in food matrices.

$$Me^{(n+1)+} + AH \rightarrow Me^{n+} + H^{+} + A^{\cdot} \qquad (2)$$

$$Me^{n+} + LOOH \rightarrow Me^{(n+1)+} + LO^{\cdot} + OH- \qquad (3)$$

Resulting in varying the reduction potential of the transition metals, separating between transition metals and hydroperoxides (LOOH), reducing the metal ions solubility, and modifying the metal ions partition in food multiphase.

Flavonoids (quercetin, rutin, morin, luteolin…) are reported for their ability to form complexation with transition metals (Fe^{2+} and Cu^{2+}). The complexation occurs with C-3 and C-5 hydroxyl groups and additionally with the dihydroxyl groups in the B ring **[25]**.

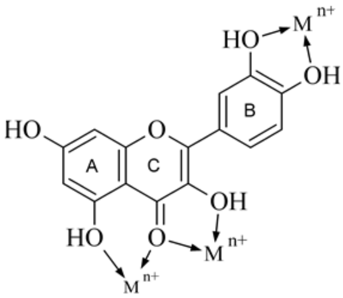

Figure 2. Metal chelator mechanism.

The blockage site C-3 of the hydroxyl group by -O-glycosylation reduces the flavonoid's bioavailability and prevents chelation. However -C- glycosylation can enhance some of its antioxidant efficiency and antibacterial properties **[26]**. In the patented antioxidants formulation **[27]**, the added soy lecithin as a source of phosphatidylcholine enhance the activity index by 4 times compared to the mixed formulation of carnosic acid (180ppm), tocopherol (1500ppm) and ascorbyl palmitate (750ppm) in commercial oil containing 18% EPA and 12% DHA. This may be not only related to the emulsion role that keeps tocopherol, carnosic acid, and ascorbyl palmitate in proximity, but also appears to participate in metal complexation. Citric acid is found in almost all types of foods. It can chelate metal ions by forming bonds between the metal and the carboxyl and or hydroxyl groups of the acetic acid molecule. Metal chelating activity is not sufficient to guarantee the antioxidant effect.

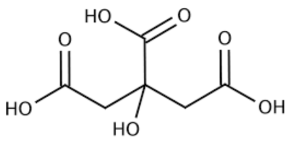

Figure 3. Molecular structure of citric acid

3.3. Singlet oxygen quenching:

The mechanisms of antioxidants with singlet oxygen quenching action mode means they can deactivate the excited state of the oxygen molecule. It can be done by deactivating the photosensitizers to prevent the activation of oxygen in the first place such as carotenoids. Carotenoids, are natural organic non-polar pigments and hold at least 40 carbons and extensively conjugated double bond system **[10]**. Carotenoids, including β-carotene, act as a singlet oxygen quencher due to the presence of a multiple conjugated double bond system. It was reported that they exhibit also radical chain breaking **[24]**.
Another mechanism is by physical quenching of singlet oxygen where the quencher enters a vibrational or electronic excited state and therefore no oxygen consumption and no formed product. Sodium azid (NaN_3) is reported to act as a physical quencher. Flavonoids also exhibit physical quenching properties, it is mainly controlled by the catechol moiety on ring B (3'-4'-dihydroxy). The absence of the carbonyl group in ring C enhances the physical quenching mode of action **[17]**.
The final action mode is chemical quenching, where the quencher reacts with oxygen. Carotenes, ascorbate, thiols, and histidine exhibit an oxygen chemical quenching mechanism **[28]**. Tournaire *et al.* (1993) **[17]** shows that the chemical quenching by flavonoid compounds is controlled by the double bond C2-C3 of ring C, examples such as quercetin and fisetin. Also, O-glycosylation reduces the flavonoid's capacity in acting as an oxygen chemical quencher.

3.4. Alkoxyl radical interruption:

Since ROOH is generated, the degradation of O-O bond needs only small energy to start. The formed hydroxyl radical is of a very reactive oxygen species.

$$LOOH \rightarrow LO^{\cdot} + {}^{\cdot}OH \qquad (4)$$

An antioxidant with alkoxyl radical action (AH) (see, eq. (5)), donate hydrogen to an alkoxyl group (LO.) and thus form a relatively stable lipid hydroxide compound (LOH). An alternative mechanism (see, eq. (6)) is that the antioxidant work as an electron donator to alkoxyl radical, which forms a terminator stable compound, antioxidant-lipid-composition (LOA).

$$LO^{\cdot} + AH \rightarrow LOH + A^{\circ} \qquad (5)$$

$$LO^{\cdot} + A \rightarrow LOA \qquad (6)$$

In this phase, no action is meaningful, since organoleptic and nutritional quality are already degraded, and every action made at this point is considered to be food fraud. Further, to set up an efficient preservation plan for each product type, a more fundamental understanding of the natural preservatives' modes of action is required.

4. Combined natural preservatives:

Since each class of natural antioxidants acts differently in food matrices, it is reasonable to use a combination of two or more antioxidants. It is anticipated that each one will contribute to stabilizing oxidation differently which turns into results getting an advantage from the potentially exhibited synergistic effects. This is not always true, since two other possible interactions may occur: additive effect and antagonism. Antioxidant synergism is a phenomenon in which the combined action of two or more antioxidants produces a stronger protective effect against oxidative stress than the sum of their individual effects. However, antagonism in the context of antioxidant effect refers to the reduction or inhibition of the protective activity of one antioxidant by another antioxidant, either directly or indirectly, resulting in a weaker overall protective effect **[19]**. The additive effect refers to the combined action of two or more antioxidants in which the protective effect against oxidative stress is equal to the sum of their individual effects **[29]**. Several methods are utilized to calculate synergism and are depending on the type of data available and the assumptions that are made about the interaction between the substances. One commonly used method is the Bliss Independence model, which assumes that the effects of the two substances are independent and additive. In this model, the expected effect of the combination is calculated as the product of the effects of the individual substances. The degree of synergy is then determined by comparing the expected effect to the actual observed effect **[29-32]**. Another method is the Loewe additivity model, which assumes that the effects of the two substances are also independent, but not necessarily additive. In this model, the expected effect of the combination is calculated based on the individual dose-response curves of each substance. The degree of synergy is then determined by comparing the expected effect to the actual observed effect **[33-34]**. Multi-synergism depends on many factors such as the concentrations/ratio of each preservative **[11]**, the temperature **[35]**, and the heterogeneity of the food system. Thus, the extrapolation of synergistic effects can be falsified without a relied test methods (Peroxide value, conjugated diene, and trienes, p-anisidine, 2-thiobarbituric acid reactive substance test (TBARS), Diphenyl-picrylhydrazyl radical (DPPH), electrospray mass spectroscopy, Raman spectroscopy, nuclear magnetic resonance, high-performance chromatography…) **[7,19,35]**.

4.1. Mixture technics of different natural antioxidants:

The health food industry needs to use fewer synthetic additives and more natural alternatives **[13]**. Many researches in the field has used plants extracts and commercial antioxidant blends, Co-incorporation (micelles, liposomes, archaesomes, nano cochleates, and other nano delivery technics…), Simultaneous extraction of a mixture of different plant species "co-extraction" and have shown a promising result **[36-38]**.

4.2. Plant extracts and commercial antioxidant blends:

Using natural antioxidants is when utilizing a plant extracted that has not been necessarily deodorized or purified. This may need a chromatography technic combined with mass spectroscopy to characterize the extracts and quantify the response yields percentage since variability can occur between plant varieties. On the other, commercialized antioxidants are for advantage a standardized content of the active ingredient, a generally qualified method of quantification of the active compounds. However, it may be expensive to generate a broad range of essays. A combination of binary natural extracts out of six groups of natural antioxidants; Licorice root antioxidant, ascorbyl palmitate, tea polyphenols, vitamin E, and rosemary extracts was investigated in microalgal DHA-rich oil. Significant synergistic effects with the binary mixture were reported for vitamin E (0.01%) / Ascorbyl palmitate (0.01%), rosemary extract (0.01%) / Vitamin E (0.01%), and rosemary extracts (0.01%) / ascorbyl palmitate (0.01%) respectively **[13]**.

In the patented formulation **[39]**, a combination of an extract from the *Labiatae* plant family and an extract from a plant of the *genus Matricaria* or of the *genus Chamaemelum* demonstrated synergistic enhancement of antioxidant activity. The Labiatae extracts are deodorized and contain from 3.5% to 70 wt.% phenolic diterpenes. The matricia/Chamaemelum extract contains flavone apigenin-7-O-glucoside or derivative there of 0.5 to 2 wt.%. the composition ratio is approximately 1:1 extract obtained from rosemary and extracts from matricia or Chamaemelum.

4.3. Co-incorporation:

Liposome encapsulation is of great interest technics mainly in the meat and meat transformation industry to preserve and release the combined active compounds. Liposomal encapsulation overcomes the shortcoming of some natural plant extracts such as pungent odor, volatility, and instability **[40]**. Also, liposomes are used in investigating the antioxidant's efficiency since they mimic the cellular structure and play the role of the model to examine the hydrophilic-hydrophobic interactions. In addition, food is considered a natural nano-structured substance, thus nanoencapsulation of bioactive is an emerging application for nanotechnology. Because of low solubility, poor chemical stability, and low bioavailability of certain antioxidants, a broad range of different types of the delivery system is developed (micelles, liposomes, archaesomes, nano cochleates, solid-lipid nanoparticles and polymer or hydrogel particle…).

A new approach to designing delivering has been reported in **[41]**, where the molecular and physicochemical properties of the active agent are well described, the required physicochemical, and sensory attributes of the end-product are defined, and the required colloidal delivery system and the particle properties are specified. The process specification, testing performance, and system optimization. Co-incorporation will not only help in creating synergism but also be of interest to the developpe of functional foods and beverages that are designed to enhance human health and wellbeing.

4.4. Simultaneous extraction of a mixture of the different plant species:

In some cases, the extraction process leads to the degradation of active compounds. Many alternatives have been reported and mixed plant extracts are of high interest, where the obtained products should be of better quality than the product obtained by mixing separate extracts. Simultaneous of mixture plant species can also contribute to the context of processing by reducing costs. This was previously observed in **[29]**, where simultaneous extraction of rosemary and spinach leaves shows additive effects of both components.

5. Conclusion:

Food preservation is an old problem that is increasing over time. Natural antioxidants and antioxidant synergism are important concepts in the field of nutrition and health as it highlights the potential benefits of consuming a variety of antioxidant-rich foods and supplements. New technologies have to be widely applied in the field, to one better understand the oxidation process. Some work has developed a model that can serve as the unified basis for understanding lipid oxidation in emulsions and therefore quantify the antioxidant effects. Secondly to investigate new incorporation systems and approaches in accordance with the required specifications of final products (Color, odor, flavor, appearance…) which may lead to including nanotechnology to help scale these solutions. Also, each food system has to be studied and characterized to investigate the potential combination of natural antioxidants needed. using a simple model system should not be extended to the potential oxidative activity and health effects. Finally, the Characterization of the degradation products, or complexes/adducts of natural antioxidants decomposition neither other oxidation products will help in targeting the right dosage, the optimized combinations, and a new basis for future analysis of lipid oxidation. Other studies provided an advanced theoretical basis for the formation of hydroperoxides and allyl from lipid oxidation at 60°C.

By working together, antioxidants can provide a more robust defense against oxidative stress and reduce the risk of chronic diseases associated with oxidative damage.

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