

**Research/Technical Note****“Speb-Pebe” - Spicy Product Energy Booster Consumer Test and Its Effects on the Consumers’ Health****Andry Tahina Rabeharitsara<sup>\*</sup>, Nambinina Richard Randriana, Ernestine Ravomialisoa**

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**Abstract:** The “spicy product energy booster (speb)” – “produit épicé boosteur d’énergie (pebe)” – “speb-pebe” was a spice food product composed mainly of “*Capsicum chinense*”, “*Capsicum frutescens*” and citric acid as active chemical molecules like preservative, catalyst and reactant. Thus, its important chemical bioactive molecules were capsaïcine, luteolin and quercetin; these molecules presented in their structure either ether and/or alcohol and/or amine and/or alkene organic functions which could reacted chemically with citric acid molecules catalyzed by citric acid protonic acid-H<sup>+</sup> to give esters, esters of citric acid, amides and amides of citric acid. These chemical reactions were very important because these citric acid derivatives forms of “speb-pebe’s” bioactive molecules facilitated their partial or total solubilization and diffusion-transport through the organism particularly through the bloodstream via chylomicrons and lymphatic system. This efficient diffusion-transport allowed to the efficiency of their therapeutic virtues through the organism which were not only developed in this manuscript but also observed through a consumer test realized on the “speb-pebe” food product during one month such as its daily consumed quantity was limited to one teaspoon which corresponded to maximally 2g of “speb-pebe” respecting its components’ bioactive molecules daily limit of consumption including quercetin, capsaïcine and luteolin. First, the results of this consumer test, realized on individuals, permitted to confirm that this “speb-pebe” food product was an energy booster. Indeed, the majority of individuals who participated in the “speb-pebe” consumption test had experienced an increase in their physical capacity and among adulthood who play sport, among student adolescent no one felt physical capacity decrease. Second, it was confirmed that the “speb-pebe” food product was classed by 43.48% of individuals as a taste and smell enhancing condiment which increased their appetite. Third, an appreciable spices’ bioactive molecules therapeutic virtues were confirmed by individuals participating this “speb-pebe” consumer test including non-detected of chronic and acute rhinitis, disappearance of psoriasis and the great majority of them felt their youth renewed; 76.20% of them were observed with normal increasing (38.10%) or stabilizing (38.10%) their weight at the end of the test without blood pressure disorder. These promising results was partly due to the probably regeneration of the chemical compound «phosphatidylserine-PS» particularly their two esters of fatty acids and an amino-acid organic functions by mechanisms described subsequently in this manuscript and the longevity of its activities as phagocyte by apoptosis where proteins probably plays significant role as citric acid protonic acid-H<sup>+</sup> catalyst support.**Keywords:** *Capsicum chinense*, “Produit épicé Boosteur d’énergie\_pebe-speb”, *Capsicum frutescens*, Citric Acid, Capsaïcine, Luteolin, Quercetin, «phosphatidylserine-PS»

## 1. Introduction

The first part of this manuscript presented the “spicy product energy booster (speb)” – “produit épicé booster d’énergie (pebe)” – “speb-pebe” mainly constituted with spices “*Capsicum chinense*”, “*Capsicum frutescens*” and citric acid as active chemical molecules like preservative, catalyst and reactant to form its esters [1]. Thus, chemical reactivity mechanisms between citric acid molecules and spices bioactive molecules catalyzed by the citric acid protonic acid-H<sup>+</sup> was presented, large part of which was viewed in bibliographies [1-6] excepting esterification reactions by ether cleavage and eventually alkene addition catalyzed also with the citric acid protonic acid-H<sup>+</sup>. Indeed, these esters forms were presented not only to facilitate the transport-diffusion of bioactive molecules but also to efficacy their therapeutic activities-vertues through the organism. The second part of this manuscript established the various therapeutic vertues of spices’ bioactive molecules including capsaïcine, luteolin and quercetine vertues according to the bibliographies. Finally, a consumer test was done with the “spicy product energy booster (speb)” – “produit épicé booster d’énergie (pebe)” – “speb-pebe” through 27 individuals statistics. This consumer test is composed of questions which permitted to evaluate, first about the testers’ satisfactions during the consumption of the product-speb-pebe as energy booster and second about the effects observed by the testers during the consumption of the product-speb-pebe. Noticed that four (4) individuals participated only on the first part of the consumer test but didn’t participate on the second part of it. The results of this consumer test was undertaken to confirm not only the organoleptic quality of the “speb-pebe” product but also the effectiveness of its therapeutic vertues based with the previous bibliographies study which in fine permitted to present mechanisms of «phosphatidylserine-PS» regenerations.

## 2. Spicy Product Energy Booster (speb) – “Produit épicé Booster D’énergie (pebe) [1]

The “spicy product energy booster (speb)” – “produit épicé booster d’énergie (pebe)” [1] was a spices food product which was mainly composed with two species of spices: the “*Capsicum chinense*” and the “*Capsicum frutescens*” and citric acids [1] as active chemical molecules like preservative [1], catalyst [1-5] and reactant [6]. This product was natural seeing that its ingredients and raw materials [1] were produced of natural products and sometimes by biological agriculture. Seeing that the main ingredients of the “spicy product energy booster (speb)” – “produit épicé booster d’énergie (pebe)” was spices [1], so this product carried the benefits of spices especially the species “*Capsicum chinense*” and the “*Capsicum frutescens*” (Table 1) not only in culinary field but also in medicinal field [7-11]. Indeed, spices were always classified among condiments which raised the taste of the

culinary preparations because of its strong spicy taste causing a strong salivation. Saliva, secreted by glands located under the ears, under the jaw and under the tongue, is essential to detect tastes and flavors by diluting the substances that give food its taste and allows them to seep into the taste buds. Saliva contained enzymes and antimicrobial and antimicrobial agents which were essential in beginning the process of digestion of dietary starches and fats; also essential for breaking down food particles entrapped within dental crevices, thus protecting teeth from bacterial decay [12-14].

**Table 1.** Scientific classifications of *Capsicum chinense* and *Capsicum frutescens*.

Scientific classifications		
Binomial name	<i>Capsicum chinense</i>	<i>Capsicum frutescens</i>
Kingdom	Plantae	Plantae
Clade	Tracheophytes	Tracheophytes
Clade	Angiosperms	Angiosperms
Clade	Eudicots	Eudicots
Clade	Asterids	Asterids
Order	Solanales	Solanales
Family	Solanaceae	Solanaceae
Genus	<i>Capsicum</i>	<i>Capsicum</i>
Species	<i>C. chinense</i>	<i>C. frutescens</i>

Spices are well known as anti-oxidants and they are excellent ways to stimulate and strengthen our immune system through the presence of quercetin up to 506mg/Kg [15-17] after the caper-1800mg/Kg and before the peppers-500.63mg/Kg. Spices also contained nutrients such as proteins 1.87g/100g-glucide 7.7g/100g-lipids 0.32g/100g, saturated and unsaturated fatty acids, and betacarotene; they are very rich in various vitamins [18].

## 3. Spices Chemical Bioactive Molecules

The chemical bioactive molecules of spices are capsaïcine and its derivatives generally named capsaïcinoïdes, luteolin and quercetin whose content is given by following table 2 [8, 15-17, 19]. The bibliography [8] gave data range of these capsaïcinoïdes and exploitation was amongst of baseline which permitted to evaluate the initial alkenes content of the spicy product energy booster (speb) – “produit épicé booster d’énergie (pebe) - pebe-spebe’s synthesis and compounds [1]. However, titration’s procedures and studies were down to evaluate the evolutions of citric acid with alkenes’ concentration and pathogenic microorganisms in the packaged spicy product energy booster (speb) – “produit épicé booster d’énergie (pebe) - pebe-spebe and also permitted to control its packaging quality [1].

### 3.1. Spices Chemical’s Bioactive Molecules Reactivity with Citric Acid Molecules

Noticed that these spices chemical bioactive molecules (Table 2) contained reactive organic functions such as amin organic function (on capsaïcine, dihydrocapsaïcine, nordihydrocapsaïcine, homodihydrocapsaïcine, homocapsaïcine – Table 2), ether organic function (on capsaïcine, dihydrocapsaïcine, nordihydrocapsaïcine,

homodihydrocapsaicine, homocapsaicine, luteolin, quercetin – Table 2), alcohol organic function (on capsaïcine, dihydrocapsaicine, nordihydrocapsaicine, homodihydrocapsaicine, homocapsaicine, luteolin, quercetin – Table 2) and alkene organic function (capsaicine, homocapsaicine, luteolin and quercetin). They not only could

reacted with citric acid molecules by esterification [5-6] and/or transesterification [3] but also supported citric acid molecules protonic acid- $H^+$  which were acid catalyst for these previous reactions including amide formation by amine function and carboxylic acid [6] and ether cleavage between an ether organic function and an carboxylic acid function (Figure 1).

Table 2. Spices chemical bioactive molecules.

chemical bioactive molecules	structures	contents [%]	contents [ $\mu\text{g/g}$ ]
Capsaicine		69% [19]	
Dihydrocapsaicine		22% [19]	
Capsaicinoïdes	Nordihydrocapsaicine	7% [19]	Cf.[8]
	Homodihydrocapsaicine	1% [19]	
	Homocapsaicine	1% [19]	
Luteolin [20, 21]		0.61-5.15mg/100g	
Quercetin [16, 17]		506mg/Kg	

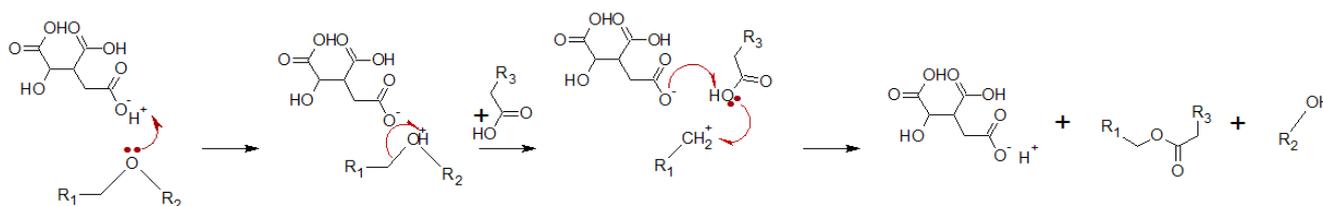
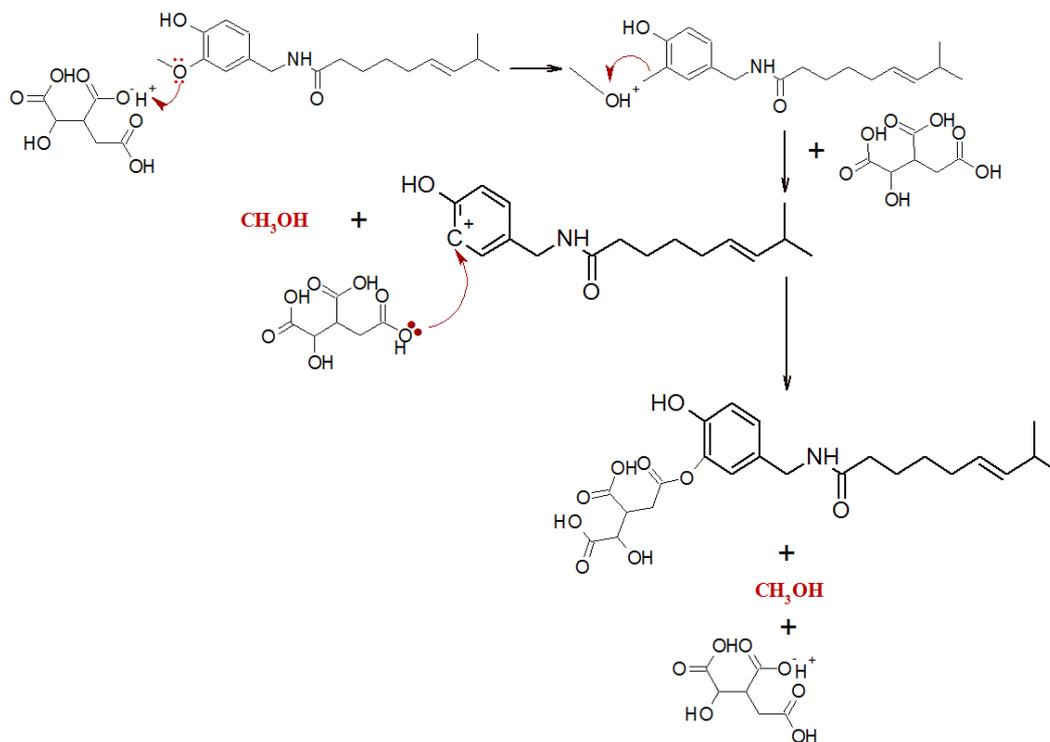


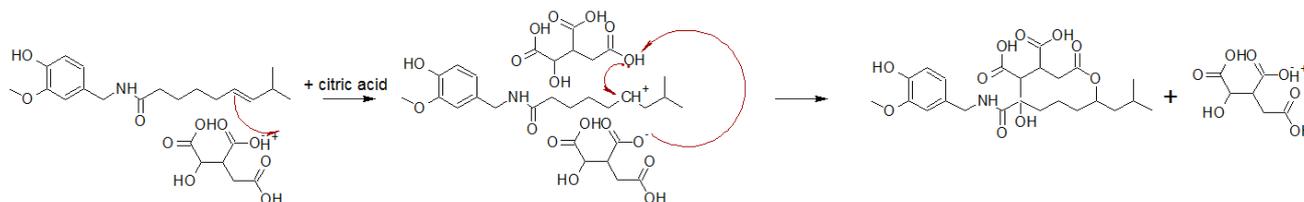
Figure 1. Ether cleavage between ether organic function and a carboxylic acid function catalyzed by citric acid protonic acid- $H^+$ .

These previous chemical reactions between citric acid molecules and spices’ chemical bioactive molecules catalyzed chemically by citric acid protonic acid- $H^+$  were very important because their products such as esters, amides of these spices chemical bioactive molecules and eventually alcohol formed were responsible of their diffusion through the human body according to the mechanism of lipid metabolism [22]; including the ether cleavage between ether organic function and a citric acid carboxylic acid function catalyzed by citric acid protonic acid- $H^+$  (figure 2) and eventually esterification of alkenes function catalyzed by citric acid protonic acid- $H^+$  (figure 3) and amide formation (figure 4).

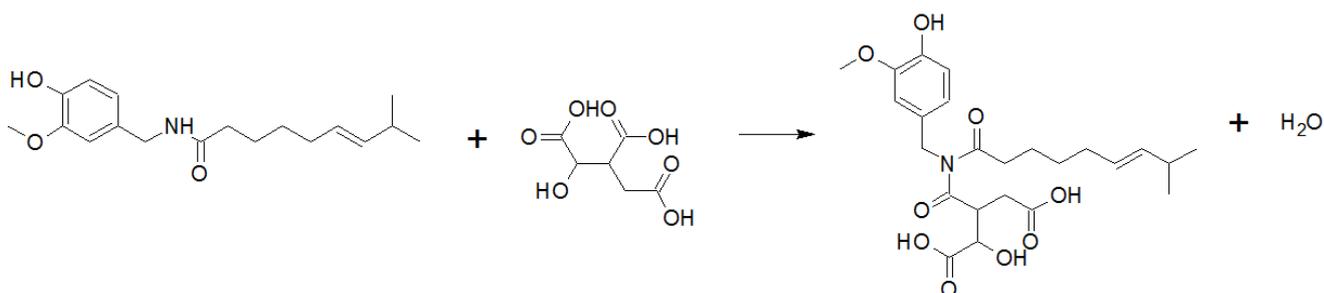
Indeed, once adsorbed these molecules derivate of citric acid (esters-amides-figure 1 to figure 4) were partially and/or totally digested into monoglyceride, fatty acids, citric acid molecules and/or stayed citric acid esters in spite of the vigorous peristalsis in the stomach and the duodenum. Then, they were solubilized in the intestine until the intestinal villi where enterocyte adsorbed them and gather them once again to triglyceride, esters and amides of citric acid and bundled with cholesterol by eventually chemical reactions [3-6] into the chylomicrons, the highest lipoproteins located into the adipose and muscular tissues. Finally, chylomicrons diffused all of them to the bloodstream via the lymphatic system.



**Figure 2.** Case of ether cleavage between capsaicin's ether organic function and a citric acid carboxylic acid function catalyzed by citric acid protonic acid- $H^+$ .



**Figure 3.** Case of esterification of capsaicin's alkene organic function with citric acid molecule catalyzed by citric acid protonic acid- $H^+$ .

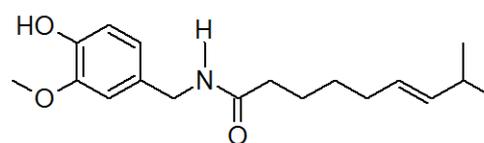


**Figure 4.** Case of amide formation with capsaicin's amine organic function and citric acid molecule.

However, it was noticed that during esterification between citric acid and *callistemon citrinus*, rice-husk, *garcinia dulcis* catalyzed by citric acid's- $H^+$ , initially, the alkenes concentrations were very important and their quantities increased until 60mn [4]. These alkenes came not only from the plants molecules but also from citric acid dehydrations [4]. Thus, the esterification of capsaicin's alkene organic function with citric acid molecule catalyzed by citric acid protonic acid- $H^+$  on figure 3 could occurred even if the capsaicin's quantities on spicy was in the range of micrograms per gram [8].

### 3.2. Spices Chemical's Bioactive Molecules and Their Therapeutic Virtues

#### 3.2.1. The Capsaicine



**Figure 5.** Capsaicine (Chemscketch).

Capsaicin is an alkaloid. Alkaloids still play an important role as active ingredient in drugs with interesting properties in pharmacology such as anti-cancer, anti-parasitic, painkillers [23]. As nasal spray, capsaicin lead to a significant long-term decrease in non-allergic and non-infectious per-annual rhinitis [24] including: - acute rhinitis manifested by edema and vasodilation of the nasal mucosa, - chronic rhinitis resulting in nasal obstruction, runny nose and headaches in patients and - vasomotor rhinitis which resulted in intermittent vascular engorgement of the nasal mucosa followed by absence of purulent discharge and crusting aggravated by dry ambient air [25]. Also, it was found that capsaicin inhibits the proliferation of *Helicobacter pylori* [26]. Noticed that *Helicobacter pylori* is an orally transmitted bacterium responsible for non-recurrent infections of the stomach with symptoms of indigestion and pain or discomfort in the upper abdomen [27]. In addition, *Helicobacter pylori* produces ammonia, which helps protect it from stomach acid and allows it to disrupt and penetrate the mucus layer which could conduct to the stomach acid-basic unbalance. Also, it was showed that capsaicin contributed to block cancer in certain lung cells or prostate cells by apoptosis [28]. Apoptosis comes from the Greek "apo-far away" and "ptosis-fall" or "programmed cell death" and is the process by which cells trigger their self-destruction in response to a signal. It is one of the possible pathways of genetically programmed physiological cell death necessary for the survival of multicellular organisms and in constant balance with cell proliferation. Thus, the transport of the capsaicin in citric acid esters form through the different organs according to the mechanism described before (§3.1.) [4-6] allowed the effectiveness of its therapeutic activities mentioned before

[3-6]. Indeed, during apoptosis the cell exposes a chemical compound «phosphatidylserine-PS» (figure 6) which is a phospholipid-amphiphilic normally constituting the internal sheet of the cell and composed chemically by two esters of fatty acids associated with a phosphate group itself associated with an amino acid.

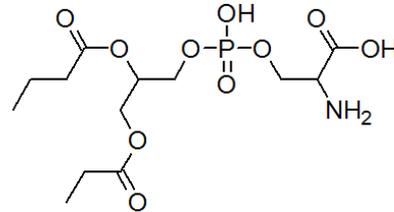


Figure 6. Phosphatidylserine-PS.

This chemical compound «phosphatidylserine-PS» would allow the phagocytosis of these cells in apoptosis; i.e. their ingestion by their equivalent phagocytes in particular white blood cells and macrophages which are molecules belonging to the white blood cells which infiltrate the tissues without circulating [29, 30]. Consequently, practically, the regeneration and the longevity of this chemical compound «phosphatidylserine-PS» was necessary and a major advantage to ensure efficiently and in long-term their activities as phagocyte. For this reason vegetable oils including peanut oil and colza oil were used as confidential [1] raw materials in the formulation of the “spicy product energy booster – ‘peb-Pebe’ ” [1] which trans-esterification catalyzed chemically by the citric acid protonic acid- $H^+$  [3] with the chemical compound’s «phosphatidylserine-PS» fatty acid esters according the mechanism on the figure 7.

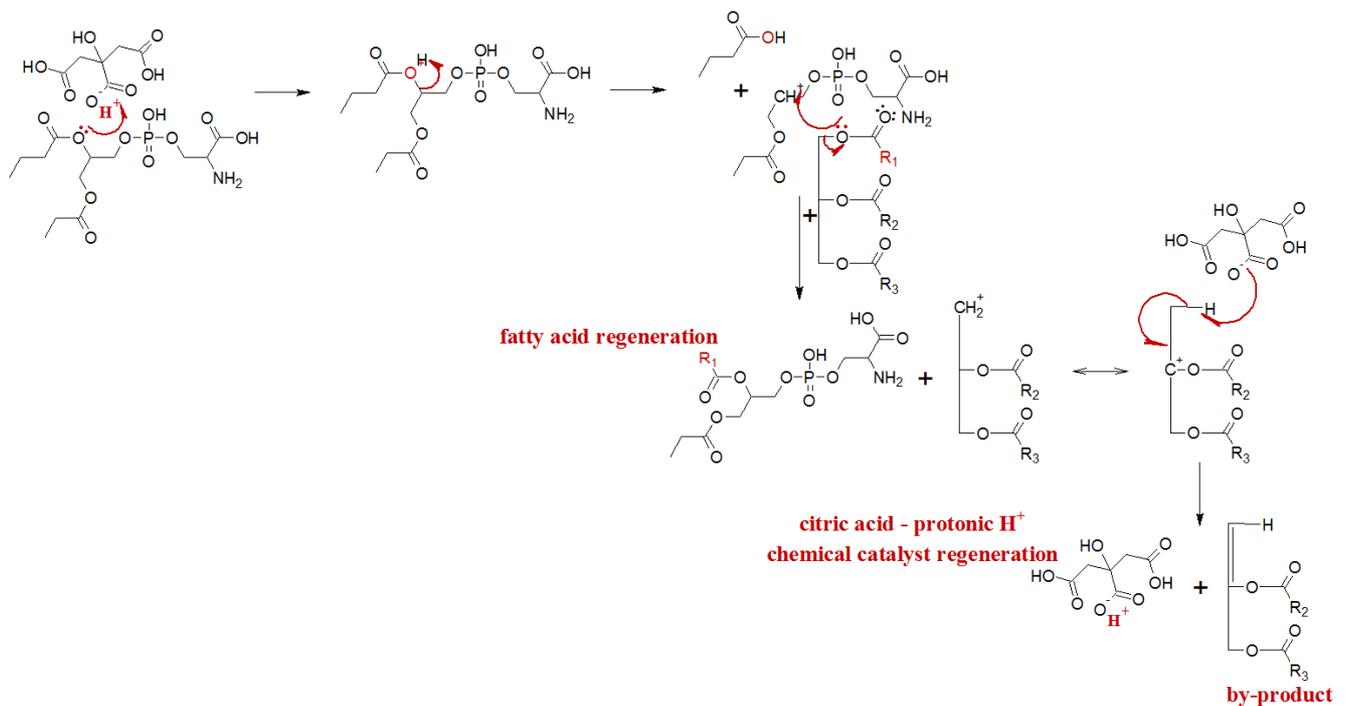
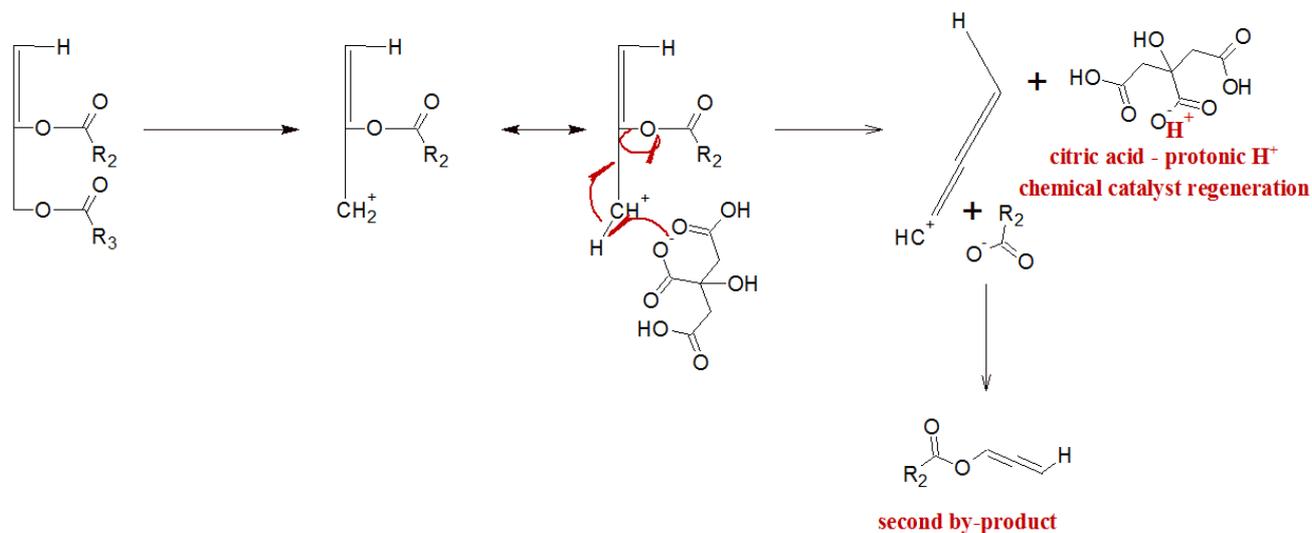


Figure 7. Fatty acid regeneration of the chemical compound’s «phosphatidylserine-PS» catalyzed by citric acid protonic acid- $H^+$ .

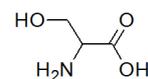
Noticed that the first by product on figure 7 could react again according to the same mechanism to regenerate another fatty acid of the chemical compound's «phosphatidylserine-PS» catalyzed by citric acid protonic acid- $H^+$  to give the second by product on figure 8.



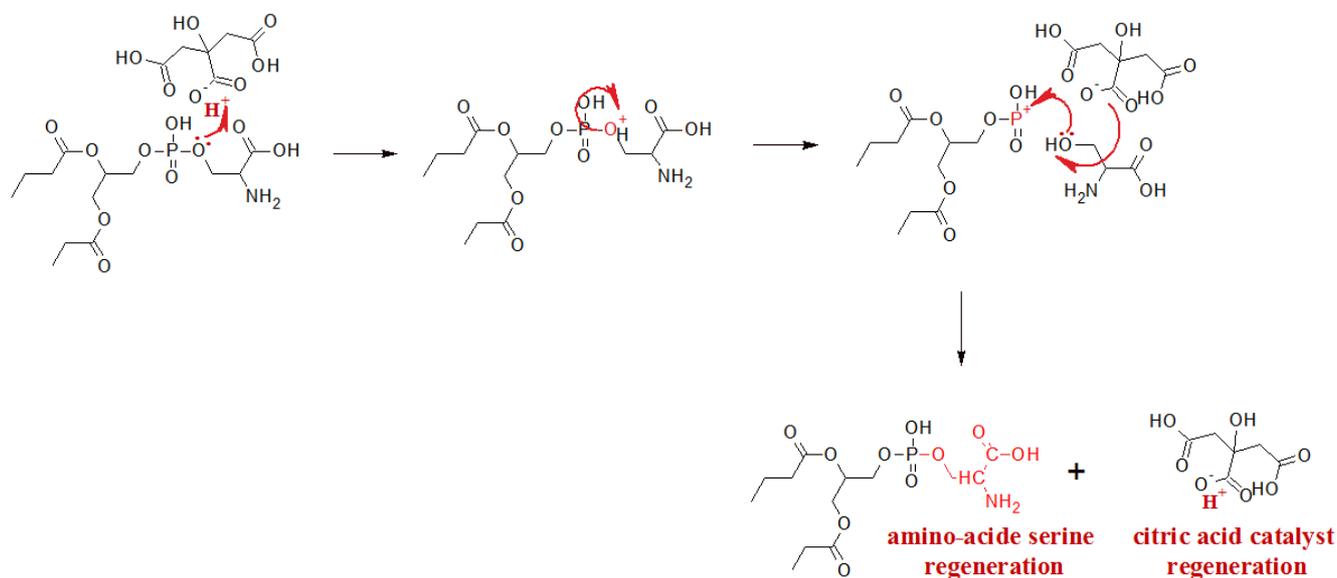
**Figure 8.** Formation of the second by-product during the participation of the first by-product (figure 7) for another fatty acid regeneration of the chemical compound's «phosphatidylserine-PS» catalyzed by citric acid protonic acid- $H^+$ .

However, another way of regeneration of this chemical compound's «phosphatidylserine-PS» esters was also possible while passing firstly by their chemical hydrolysis catalyzed by citric acid protonic acid- $H^+$  [6] followed thereafter by a trans-esterification with the oil's fatty acids always catalyzed chemically by citric acid protonic acid- $H^+$  [3]. Thus, the serine compound [31] (figure 9) of the phosphatidylserine could also

be regenerated by trans-esterification according the mechanism described on figure 10.



**Figure 9.** Amino-acid Serine.



**Figure 10.** Amino-acid - case of the chemical compound's «phosphatidylserine-PS» "Serine" - regeneration catalyzed by citric acid protonic acid- $H^+$ .

Note that serine is cited by bibliographies as one of the most abundant amino acids in organisms [32], thus promoting muscle development, preserving cognitive functions and combating concentration problems [32]. Serine is also used in the synthesis of other amino acids including glycine, cysteine

and tryptophane [32] and stimulated the fat metabolism according to a biosynthesis mechanism [33]. Finally, note that capsaïcine was used as active ingredient in the medicine ZOSTRIX which can relieve violent pruritus, arthritic pain and some chronic neuropathic pain [34].

### 3.2.2. The Luteolin

The Luteolin (figure 11) is an anti-inflammatory and an anti-allergic flavonoid [35], an anti-oxidant and a vasorelaxant [36], a strong inhibitor of abnormal angiogenesis of cancer cells [37]. The luteolin is also a caspase-7 activator, inducing apoptosis of colon cancer cells [38] and an antidiabetic by inhibition of alpha-amylase and alpha-glucosidase [39]. It has a significant antimicrobial activity against *Staphylococcus aureus* [1, 40] and a therapeutic effect on chronic inflammatory bowel disease (IBD) [16]. Thus, the transport of the luteolin in citric acid esters form through the different organs according to the mechanism described before (§3.1.) [4-6] allowed the effectiveness of its therapeutic activities mentioned before [3-6].

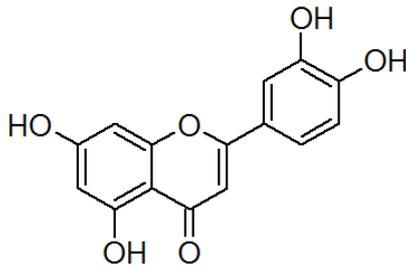


Figure 11. Luteolin (Chemsketch).

### 3.2.3. The Quercetin or Quercetol

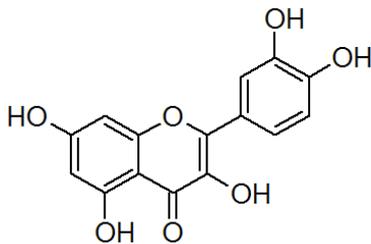


Figure 12. Quercetin – quercetol (Chemsketch).

Quercetin (figure 12) is an antioxidant that protects cells from free radicals, it is the most powerful scavenger of reactive oxygen species ROS (or free oxygen radicals) [41]. Kampkotter and colleagues (2008) show that quercetol treatment of *Caenorhabditis elegans* worms increases their resistance to oxidative stress and extends their lifespan by 15 percent [42]. Quercetin is also an antimutagenic [43] and Edwards *et al.* (2007) noted an improvement in blood pressure in hypertensive subjects after taking quercetol daily for four weeks [44]. Baugman *et al.* (2003) on patients suffering from sarcoidosis, a chronic inflammation of the lungs accompanied by oxidative stress, showed an improvement of the antioxidant system after taking quercetol [45]. Treatment of patients suffering from chronic prostatitis with quercetol provided a significant improvement of their symptoms [46]. Thus, the transport of the quercetin in citric acid esters form through the different organs according to the mechanism described before (§3.1.) [4-6] allowed the effectiveness of its therapeutic activities mentioned before [3-6].

### (i). Quercetin and TNF $\alpha$ (Tumor Necrosis Factor Alpha) Inhibition

Quercetin inhibits the production of TNF $\alpha$  [47] seeing that bibliographies showed that the dysregulation of TNF $\alpha$  production has been implicated in a range of human diseases such as "Alzheimer's disease" [48], cancer [50], depression [50], psoriasis [51] and chronic inflammatory bowel disease (IBD) [52]. TNF $\alpha$  is a protein essentially produced by activated macrophages. These macrophages are cells belonging to the white blood cells that infiltrate the tissues. Thus, logically, the blocking or inhibition of TNF $\alpha$  production by quercetin mentioned previously should be accompanied by an increase or at worst a stagnation not only of the macrophages' TNF $\alpha$  concentration but also of the number of white blood cells and its very important components for the immune system. In fact, the white blood cells components essentially auxiliary T lymphocytes, NK lymphocytes, neutrophil granulocytes, eosinophil granulocytes, the mast cell increased or at worst stagnate due to this inhibition of TNF $\alpha$  by the quercetin and boosted the immune system. Indeed, firstly *auxiliary T cells*, sometimes called *non-cytotoxic T cells*, are at the center of the adaptive immune response, proliferating only when they recognize certain pathogenic antigens presented by an antigen presenter cell; seeing that an antigen is a natural or synthetic macromolecule that is recognized by antibodies of the immune system the cells of an organism and is capable of initiating an immune response. Secondly, *NK lymphocytes or natural cytotoxic lymphocytes*, also called natural killer cells, have intrinsic and innate anti-tumor properties and reside in several lymphoid and non-lymphoid tissues including bone marrow, lymph nodes, skin, intestine, tonsils, liver and lungs [53]. Thirdly, *Neutrophilic granulocytes or PNN-polynuclear neutrophils* are blood cells belonging to the white line. In fact, these are white blood cells (leukocytes) that have a major role in the immune system. The passage of PNN-polynuclear neutrophils in the blood is rapid and brief because they play their role mainly in the tissues where they are the main cellular anti-bacterial agent. The life time of the PNN-polynuclear neutrophils in the blood is very short because it is entirely consumed by its function, which contributes to make it an absolutely non-specific anti-infection cell. Thus, the PNN-polynuclear neutrophils can combat a very wide variety of different threats [54-57]. Neutrophils alone represent about 65% of all leukocytes in the blood and 99% of granulocytes. Fourth, *eosinophilic granulocytes or eosinophilic polynuclear cells* are white line blood cells present in all vertebrates; they are involved in the innate immune system, particularly in allergy and parasitism phenomena. Fifth, the *mast cell* is a cell found in connective tissue and is characterized by the presence in its cytoplasm of numerous granulations containing chemical mediators such as serotonin, histamine, tryptase or heparin, which is degranulated and released in the presence of or in contact with an allergen, parasites or bacteria [58-60]. At the level of the nervous system, the mast cell is an innate and adaptive immune system playing the role of regulator of allergic responses [61]. In addition, it is through the mast cell

that pathogens could stimulate the gut brain axis [62-64]. The gut brain axis (GBA) is a bidirectional link between the central nervous system (CNS) and the enteric nervous system (ENS) of the body. It involves direct and indirect pathways between cognitive and emotional centers in the brain with peripheral intestinal functions. Also, the gut brain axis involves complex crosstalk between the endocrine (hypothalamic-pituitary-adrenal axis), immune (cytokine and chemokines) and the autonomic nervous system (ANS) [64, 65]. Although controversial, some studies of depression and IBD link these conditions to high levels of TNF $\alpha$  [66, 67]. Described in another way, TNF $\alpha$  activity in the body triggers leukocyte regulation by activating fever, apoptosis and cachexia (profound weakening of the body related to severe undernutrition). Cachexia is not a disease and an end in itself but the beginning of an inflammation leading the organism to an anti-viral replication.

### (ii). Quercetin and Interleukin-8 IL-8 Inhibition

Quercetin also inhibits IL-8 production in lung cells [41]. IL-8 is a chemokine produced by macrophages and other cells including epithelium cells and endothelial cells. Firstly, *Epithelium tissues* were a thin, continuous, protective layer of cells composed with the *epithelium cells*. The epithelium tissues line the outer surfaces of organs and blood vessels throughout the body, as well as the inner surfaces of cavities in many internal organs. An example is the epidermis, the outermost layer of the skin [68]. Epithelial layers contain no blood vessels, so they must receive nourishment via diffusion of substances from the underlying connective tissue, through the basement membrane [69]. Cell junctions, consisting of multiprotein complexes that provide contact or adhesion between neighboring cells or between a cell and the extracellular matrix in animals, are especially abundant in epithelial tissues [70]. Secondly, *endothelial cells* line the entire blood vessels circulatory system as a single cell layer that regulates exchanges between the bloodstream and the surrounding tissues. Signals from endothelial cells organize the growth and development of connective tissue cells that form the surrounding layers of the blood-vessel wall [71]. Endothelial cells stock their IL-8 in the Weibel-Palade Bodies which in turn store two principal molecules, P-selectin and Von Willebrand factor. These two agents play a role in inflammation and hemostasis [72]. Von Willebrand factor is essential for blood coagulation [73]. P-selectin plays a major role in the ability to increase the permeability of endothelial cells, permitting the components of the cell-mediated immune system (leukocytes) to roll, marginate, and enter the extracellular focus of inflammation. Thus, inhibition of IL-8 by quercetin should be logically accompanied by an increase or at worst a stagnation not only of the WPB's IL-8 concentration but also of the number of the epithelium cells and endothelial cells like that occurred during the inhibition of TNF $\alpha$  (§3.2.3.1) and increased the focus of inflammation penetration by active molecules and enzymes. But, noticed that this inhibition logically may be accompanied with an increasing activities of the P-selectin and the Von Willebrand

factors; especially P-selectin also plays a role in platelet aggregation, as it is activated and transported into the cell membrane by thrombin enzyme [73]. Thrombin is a naturally occurring enzyme that converts fibrinogen into fibrin, which is an integral step in clot formation. In vivo thrombin is formed from prothrombin as a result of activation of both the intrinsic and extrinsic pathways of the coagulation cascade [74]. Thus, bibliographies showed the harmful effects of prolonged opening of the endothelium and dysfunctional activities of P-selectin and Von Willebrand factors such as obesity, swelling of tissues (oedema), inflammations due to the activation of Transcriptor-TFs factors in particular AP-1 and NF-kB leading to an increase in the expression of cytokines such as IL-1, TNF $\alpha$  and risks of cardiovascular problems [75-82]. As said previously, quercetin inhibits particularly IL-8 production in lung cells [41] and in the same time inhibits TNF $\alpha$  production. Thus, logically the lung's macrophages cells including neutrophils and eosinophils quantities increased promoting the lung-organism defenses against infections, allergic reactions, asthma and parasitic infections. Indeed, bibliography said that human bronchial epithelial cells (BEC) play a major role in the immune or inflammatory responses of the lower airway mucosa [83]. BEC not only constitute a physiological barrier against pathogens but also participate in the recruitment of immuno-effective cells such as neutrophils and eosinophils [84-87].

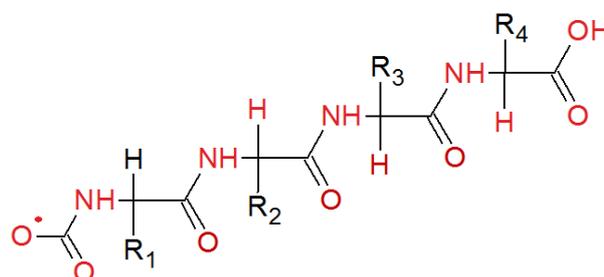


Figure 13. Protein Primary structure (Chemskech).

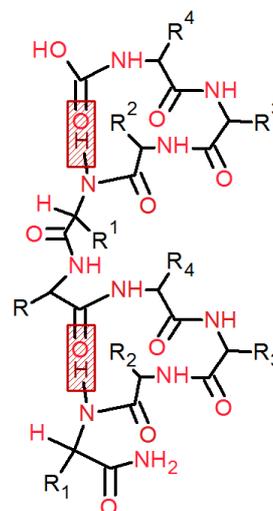


Figure 14. Protein secondary  $\alpha$ -helix structure of Pauling Corey Branson (Chemskech).

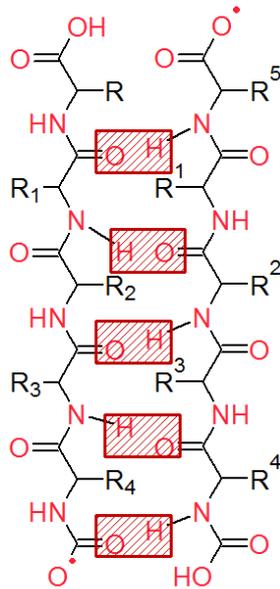


Figure 15. Protein secondary parallel  $\beta$ -sheet structure (Chemsketch).

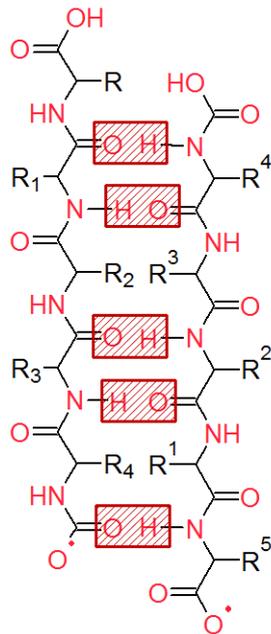


Figure 16. Protein secondary anti-parallel  $\beta$ -sheet structure (Chemsketch).



Figure 17. Tertiary structure of a whole protein molecule.

### (iii). Interleukin-8 IL-8 and TNF $\alpha$ Structure Effects

Interleukin-8 IL-8 and TNF $\alpha$  are chemotactic cytokines that control the migration and the location of immune cells. Chemically, they are composed with soluble proteins and

glycoproteins which were formed with sequential chain of amino acid. They can be presented under several structures including first the *primary structure* in straight line (figure 13), second the *secondary structure* which can be either in  $\alpha$ -helix of Pauling Corey Branson (figure 14), or in parallel (figure 15) or anti-parallel  $\beta$ -sheet (figure 16), third there is the *tertiary structure* (figure 17) and finally the *quaternary structure* formed by several protein molecules (polypeptide chains), usually called protein subunits in this context, which function as a single protein complex and *quinary structure* which is the signatures of protein surface that organize the crowded cellular interior. Quinary structure is dependent on transient, yet essential, macromolecular interactions that occur inside living cells. [88].

What is alike these various protein's structures is that they are constituted not only by several side by side oxygens and hydrogens atoms but also constituted of functional groups alkyl with or without alkene organic function according to the original nature of the amino acids' side chains which compose these proteins [31]. These clusters of oxygen and hydrogen atoms would be even more important for the beta-sheet structure (figure 15 – figure 16) observed for proteins in many human diseases including amyloidosis like Alzheimer and cardiac muscle disease [48, 50, 77-79]. However, the literatures showed that these electrons pairs carried by alkenes and oxygen atoms with hydrogen atoms served as an effective support by hydrogen bond for chemically active catalytic and transporter molecules such as sulfuric acid and citric acid [1-5]; citric acid which have been cited before as reagent and catalyst for «phosphatidylserine-PS» regeneration (§3.2.1) with active molecules' esterification and then their efficient transport in citric acid esters form through the different organs according to the mechanism described before (§3.1.) [4-6] allowed to the effectiveness of their therapeutic activities mentioned before (§3.) [3-6]. In this case, these therapeutic active molecules described previously are spices chemical's bioactive molecules including capsaïcine, luteolin and quercetin (§3.2.) which were, with citric acid, the main ingredients of the “spicy product energy booster (speb)” – “produit épicé boosteur d'énergie (pebe)” [1].

Thus, a consumer test had been carried out on the product - the “spicy product energy booster (speb)” – “produit épicé boosteur d'énergie (pebe)” [1].

## 4. “Spicy Product Energy Booster (speb)” – “Produit Epicé Boosteur D'énergie (pebe)” Consumer Test

This consumer test is composed of questions which permitted to evaluate, first about the testers' satisfactions during the consumption of the product-speb-pebe as energy booster and second about the effects observed by the testers during the consumption of the product-speb-pebe. But, before the following paragraph presented the statistical individuals.

#### 4.1. Statistical Individuals Characteristics of Consumers Participating This “speb-pebe” Consumer Test

Noticed that the statistical individuals was mainly composed of man (85.19%). The students represent 25.93% and active adulthood represent 70.37% seeing that individuals more than 50 olds are also active. The majority of the

individuals practice sports (62.96%) but they expend energy either physically or intellectually during their work and/or hobbies. Before this “speb-pebe” consumer test, the great majority of individuals (96.30%) consumed either spices either only products with spice (11.11%) but only 32% consumed them frequently. The majority of the individuals who consumed spices took it at lunch (81.48%) (Table 3).

Table 3. Statistical individuals characteristics.

Number of individuals	27				
sex	man 85.19 [%]		women 14.81 [%]		
Age [%]	[15-19] 3.70	[20-24] 25.93	[25-30] 25.93	[40-49] 29.63	>50 14.81
social categories [%]	student - adolescent 29.63		adulthood 70.37		
sports activities practice [%]	yes 62.96		no 37.04		
weight – [kg] (before the consumer test) [%]	[40-44] 3.70	[45-49] 7.41	[50-54] 18.52	[55-59] 7.41	>60 62.96
chronic disease [%]	yes 14.81		no 85.19		

Individuals spice consumptions characteristics before the consumer test			
spice and/or products with spice consumption [%]	individuals consumer 96.30	individuals non-consumer 3.70	
consumption frequency [%]	frequently 32	sometimes 40	few 28
meal spice consumption [%]	lunch 81.48		snack-grills 14.81
types of spicy products consumed [%]	spicy manufactured products 37.04		raw spice 14.81
		chilies in sauce 37.04	

#### 4.2. “Spicy Product Energy Booster (speb)” – “Produit épicé Boosteur D’énergie (pebe)” Consumer Test Results as Energy Booster Product

First of all, it’s important to note that this consumption test was carried out for one month and the daily consumed quantity of the “speb-pebe” was limited to one teaspoon

which corresponded to maximally 2g of “speb-pebe” respecting its components’ bioactive molecules daily limit of consumption including quercetin, capsaicin and luteolin. Thus, the effects felt by the individuals during “spicy product energy booster (speb)” – “produit épicé boosteur d’énergie (pebe)” consumption for one month was shown in the following tables 4-7.

Table 4. Global physical capacity of individuals participating the “speb-pebe” consumer tests.

Physical capacity	visual capacity decrease	physical capacity increase	physical capacity decrease
Percentage [%]	4.35	56.52	8.7

Table 5. Global heath sensation of individuals participating the “speb-pebe” consumer tests.

Health sensation	sleep disorder	improved sleep	stable sleep	tingling sensation
Percentage [%]	4.35	26.09	34.78	8.7

Table 6. Individuals participating the “speb-pebe” consumer tests asserting an increase of their physical capacity.

Physical capacity increase	among those who play sport	among those who don’t play sport
Percentage [%]	47.06	50

Table 7. Global consumer test results concerning physical capacity and tingling sensation of social categories and sport activity practice group.

Groups	Consumer Test Results		
	Felt physical capacity increase	Felt physical capacity decrease	Felt tingling sensation
Among student - adolescent [%]	25	0	0
Among adulthood [%]	57.89	10.53	10.53
Among adulthood who play sport [%]	54.55	0	0

Looking at these results in Tables 4-7, the majority of individuals who participated in the “speb-pebe” consumption test had experienced an increase in their physical capacity and among adulthood who play sport, among student adolescent no one felt physical capacity decrease. Among individuals who felt an improved sleep, only 16.67% ate spices frequently before this consumer test and the great majority of them have respected the daily consumption doses. In the other word, the respect of the daily consumption doses could lead to improve sleep especially the only individual who had noticed a sleep disorder consumed very few spicy products and/or spices before the consumer test. Also, it was noticed that the individuals who felt tingling sensation was among adulthood who play sport (10.53%) but they didn’t felt physical capacity increase; according to their job this tingling sensation was certainly due to their working condition. Concerning the student-adolescent who noted a visual capacity decrease, he didn’t have chronic disease and consumed few spices and/or spices products before the consumer test but have consumed the product more than the daily consumption doses during the one month consumer test, however his cholesterol stayed stable. Thus, this visual disorder couldn’t be directly associated with “speb-pebe” consumption. Concerning the two individuals who felt physical capacity decrease (8.70%), they consumed few spices and/or spices products before the one month consumer test and one have a chronic disease with a particular working condition; in addition they didn’t play sport. In brief, it was ascertained that this “spicy product energy booster (speb)” – “produit épicé boosteur d’énergie (pebe)” was a food complement increasing and boosting energy indeed accompanied with sport and manageable workload.

In the following paragraph (§4.3.), the relations between the spices’ bioactive molecules therapeutic virtues described on the previous paragraph (§3.) and the consumption of the “spicy product energy booster (speb)” – “produit épicé boosteur d’énergie (pebe)” were viewed.

#### **4.3. “Spicy Product Energy Booster (speb)”–“Produit épicé Boosteur D’énergie (pebe)” Consumer Test Results and Its Bioactive Molecules Therapeutic Virtues Relation**

Noted that 71.43% of individuals participating the “speb-pebe” consumer test affirmed that it has a very spicy taste and smell, 43.48% and 26.09% of them claimed having an increase of respectively appetite and the desire to drink water; these results confirmed the quality of “speb-pebe” as a taste and smell enhancing condiment [7-12, 14]. Seeing that the main raw material of the “speb-pebe” was spices, thus it inherited their virtues such as an anti-oxidant which stimulated and strengthened our immune system through their components bioactive molecules [15-17] (§2.). Individuals participating the “speb-pebe” consumer test didn’t presented the symptoms of chronic rhinitis and acute rhinitis including edema, vasodilation of the nasal mucosa (0%), nasal obstruction (0%), runny nose accompanied with headache (0%), in addition the great majority (100%) of individuals claimed clearly not having nasal obstruction nor runny nose with headache; these results confirmed the activity of

capsaicine bioactive molecules therapeutic virtues [24] (§3.2.1.). It was noted that 19.23% of this consumer test individuals, whose 20% didn’t consume spices and 80% consumed very few spices and/or spiced products before this “speb-pebe” consumer test, presented at the beginning of the test simple upset stomach accompanied sometimes with diarrhea. It was certainly due to the capsaicin of the spices’ “speb-pebe” and its citric acid molecules which could inhibits rapidly the proliferation of *Helicobacter pylori* [26] and other micro-organism pathogens [1] in stomach accompanied certainly with stomach acido-basic balance disorder initially (§3.2.1.). Among of the 14.81% of individuals presenting chronic disease before the “speb-pebe” consumer test (table 3), there was having the psoriasis disease which disappeared at the end of the test; it was probably due not only to the efficiency of “speb-pebe’s” quercetin bioactive molecule [52] (§3.2.3.1.) but also due to the regeneration and the longevity of the chemical compound «phosphatidylserine-PS» according to the mechanisms on figure 7 to figure 10 benefits were important as described previously on paragraph §3.2.1 with also the positive effects of the others bioactive molecule including luteolin and quercetin described respectively on paragraphs §3.2.2 and §3.2.3.. Indeed, the great majority of the individuals participating the “speb-pebe” consumer test felt their youth renewed; 76.20% of them were observed with normal increasing (38.10%) or stabilizing (38.10%) their weight at the end of the test within blood pressure disorder; 4.35% have even observed a decrease of blood pressure and some of them observed their cholesterol (8.70%) and blood pressure (8.70%) stabilized. Among adulthood who plays sport, 54.55% of them felt their physical capacity increasing (tables 4-7). But, another possible explanation of the two individuals who felt physical capacity decrease (8.70%) (On paragraph §4.2) was, seeing that they consumed few spices and/or spices products before the one month consumer test, the effect of quercetin on TNF $\alpha$  dysregulation (described on paragraph §3.2.3.1) could activate fever, apoptosis and cachexia (profound weakening of the body related to severe undernutrition). Cachexia which isn’t a disease and an end in itself but the beginning of an inflammation leading the organism to an anti-viral replication [47-67]. These better results were largely due not only to the respect of the daily consumption doses during the one month consumer test but also due to the efficiency of citric acid molecules to esterify all “speb-pebe’s” bioactive molecules according to the mechanisms described on figure 1 to figure 4 (§3.1.) catalyzed by citric acid protonic acid-H<sup>+</sup> [3-6] which activities could be improved by the Interleukin-8 IL-8 and TNF $\alpha$  structure effects composed with Oxygen, hydrogen atoms with alkenes organic functions of proteins’ R-alkyl as catalyst-citric acid protonic acid-H<sup>+</sup> support [2, 5] by hydrogen bond (§3.2.3.3.). Finally, it was noticed that 8.70% of the individuals who ate very few spices before this “speb-pebe” consumer test presented punctual red spots at the beginning of “speb-pebe” consummation certainly due to the mechanism of prolonged opening of the endothelium and dysfunctional activities of

P-selectin and Von Willebrand factors following Interleukin-8 IL-8 inhibition by quercetin conducting to obesity, swelling of tissues (oedema), inflammations (§3.2.3.2) [75-82]. But, certainly due to the respect of the daily consumption doses of “speb-pebe”, there were any cardiovascular problem.

## 5. Conclusion

The “spicy product energy booster (speb)” – “produit épice boosteur d’énergie (pebe)” – “speb-pebe”, consumed daily with one teaspoon corresponding to maximally 2g of “speb-pebe”, was a real taste and smell enhancing condiment which could increase physical capacity and promote good health. Indeed, 54.55% of adulthood who played sport claimed an increasing of their physical capacity and no one of student-adolescent claimed their physical capacity decreased. It was studied and observed in this manuscript that these results were mainly based firstly on spices’ chemical bioactive molecules including capsaïcine, luteolin, quercetin molecules and secondly oils, including the high quality colza and peanuts oils used in the “speb-pebe” synthesis [1], which regenerated and sustained the «phosphatidylserine-PS» activities. Firstly, these bioactive molecules in esterified forms with the citric acid molecules in the “speb-pebe”, including esters and/or amides of citric acid, were partially digested then easily solubilized in the intestine where certainly a part of them could be regenerated chemically in the previous citric acid esters and/or amides forms and transported-diffused through the organism by bloodstream via the lymphatic system, consequently they were able to practice efficiently their therapeutic vertues in the corresponding organs. Thus, it was observed that the great majority (100%) of individuals claimed clearly not having chronic and acute rhinitis like nasal obstruction nor runny nose with headache. As said previously, it was observed that the physical capacity increased which could correspond to the increase of the numbers and concentration of white blood cells via the TNF $\alpha$  and Interleukin-8 IL-8 inhibition by quercetin molecules mechanism which consequently played a very important role for the immune system. And also, it was observed a disappearance of psoriasis disease and the great majority of individuals felt their youth renewed. Secondly, the longevity and the efficiency of the «phosphatidylserine-PS» were possible by the regeneration of their organic functions principally their two esters of fatty acids and the amino-acid organic functions by mechanisms described previously in this manuscript. Thus, these «phosphatidylserine-PS» could sustained their phagocyte activities by apoptosis and could explained not only the stabilization and/or the increasing of 76.20% individuals’ weight but also their youth renewed. Finally, it is important to note that all these previous chemical reactions shall be made very efficient and conducted to these promising results mainly under the effect of the citric acid protonic acid-H<sup>+</sup> catalyst based on the mechanisms described previously which activities were certainly optimized and increased under the effect of not only the TNF $\alpha$  and Interleukin-8 IL-8 structures but also probably the other proteins structures of fit or sick human as studied previously presenting oxygen, hydrogen atoms with alkenes organic

functions of proteins’ R-alkyl as catalyst-citric acid protonic acid-H<sup>+</sup> support [2, 5] by hydrogen bond (§3.2.3.3.). However, it was also noted that very few individuals (8.70%) felt body pain and (8.70%) felt physical capacity decrease, mainly in relation with their work conditions, but it could be proposed to drink occasionally and gradually hot water citrus solution sweetened reasonably according to their health in relation to sugar and its derivatives.

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## References

- [1] Nambinina Richard Randriana, Ernestine Ravomialisoa, Andry Tahina Rabearitsara “Washing-Disinfectant Product Synthesis Tested During the Production of the “Speb-Pebe” - Spicy Product Energy Booster Characterized by Established Titration Procedures” American Journal of Applied Chemistry Volume 9, Issue 3, June 2021, Pages: 53-64 Received: May 17, 2021; Accepted: May 29, 2021; Published: Jun. 21, 2021.
- [2] Nambinina Richard Randriana, Rovatahianjanahary Behevitra, Andry Tahina Rabearitsara: “Pine Wood Powder Treatment to B<sub>x</sub>H<sup>+</sup> Homogeneous Catalyst (H<sup>+</sup>/H<sub>2</sub>SO<sub>4</sub>) Supported on Its Aromatics’ and PNA’ Alkenes – Application in Black Citric Acid Polymer Synthesis”, American Journal of Polymer Science and Technology - Volume 4, Issue 1, March 2018, Pages: 1-27 - Chemical Process Engineering Department (E. S. P. A), Antananarivo University, Antananarivo, Madagascar.
- [3] Nambinina Richard Randriana, Raherimandimby Joachim, Andry Tahina Rabearitsara: “Trans-Esterification Between Citric Acid and Peanut Oil at Low pH and Ambient Temperature Catalyzed by Citric Acid and Sulfuric Acid Protonic Acid-H<sup>+</sup>”, American Journal of Applied Chemistry - Volume 8, Issue 4, August 2020, Pages: 100-116 - Chemical Process Engineering Department (E. S. P. A), Antananarivo University, Antananarivo, Madagascar.
- [4] Nambinina Richard Randriana, Sedraniaina Domoina Marie Esperance, Randriamanantena Ny Idealy Elite, Mampitefa Raïssa Faneva,, Andry Tahina Rabearitsara: “Esterification Between Citric Acid and Callistemon citrinus, Rice-Husk, Garcinia dulcis Catalysed by Citric Acid’s-H<sup>+</sup>- Monomers and Polymers Formation Mechanism”, American Journal of Applied Chemistry - Volume 8, Issue 2, April 2020, Pages: 31-54 - Chemical Process Engineering Department (E. S. P. A), Antananarivo University, Antananarivo, Madagascar.
- [5] Nambinina Richard Randriana, Ratsimba Marie Hanitrianiaina, Rakotomalala Alain Fabrice, Rakotosaona Rijalalaina,, Andry Tahina Rabearitsara: “Synthesis of Glues with Citric Acid and Sulfuric Acid Protonic Acid-H<sup>+</sup> as Catalysts Using Banana Peel and Kaki as Valorised Raw Materials” American Journal of Applied Chemistry Volume 9, Issue 1, February 2021, Pages: 21-35 Received: Jan. 14, 2021; Accepted: Jan. 22, 2021; Published: Jan. 28, 2021 - Chemical Process Engineering Department (E. S. P. A), Antananarivo University, Antananarivo, Madagascar.

- [6] Nambinina Richard Randriana, Raharilaza Paulin Merix, Andry Tahina Rabeharitsara: “Esterification Between Citric acid and Pumpkin Pips’ Organic Molecules – Esters Hydrolysis And Esters Used as Hydrocarbons Additives”, American Journal of Applied Chemistry - Volume 6, Issue 3, June 2018, Pages: 78-95 - Chemical Process Engineering Department (E. S. P. A), Antananarivo University, Antananarivo, Madagascar.
- [7] Robert Jarret, Terry Berke, Elizabeth A Baldwin, George Antonious: “Variability for Free Sugars and Organic Acids in Capsicum chinense” - March 2009, Chemistry & Biodiversity 6 (2): 138-45, doi: 10.1002/cbdv.200800046.
- [8] George F. Antonious “Capsaicinoids and Vitamins in Hot Pepper and Their Role in Disease Therapy” Submitted: January 16th 2018 Reviewed: May 2nd 2018 Published: November 5th 2018, DOI: 10.5772/intechopen.78243.
- [9] “Capsicum chinense” Jacq. The Plant List.
- [10] Carl Linnaeus (Carl von Linné) (1707-1778).
- [11] Carvalho, S. I. C.; Ragassi, C. F.; Bianchetti, L. B.; Reifschneider, F. J. B.; Buso, G. S. C.; Faleiro, F. G. (2014-09-12). "Morphological and genetic relationships between wild and domesticated forms of peppers (*Capsicum frutescens* L. and *C. chinense* Jacquin)" Genetics and Molecular Research. 13 (3): 7447–7464. doi: 10.4238/2014. September. 12. 11. ISSN 1676-5680. PMID 25222244.
- [12] Nosek, Thomas M. "Section 6/6ch4/s6ch4\_6". Essentials of Human Physiology. Archived from the original on 2016-01-17.
- [13] Edgar, M.; Dawes, C.; O'Mullane, D. (2004). *Saliva and Oral Health* (3 ed.). British Dental Association. ISBN 978-0-904588-87-3.
- [14] Fejerskov, O.; Kidd, E. (2007). *Dental Caries: The Disease and Its Clinical Management* (2nd ed.). Wiley-Blackwell. ISBN 978-1-4051-3889-5.
- [15] “Les aliments riches en quercetine” <https://conseils-naturels.com/aliments-riche-quercetine/>
- [16] Département de l'Agriculture des États-Unis, «USDA Database for the Flavonoid Content of Selected Foods» [archive], sur <http://www.nal.usda.gov> [archive], National Agricultural Library, 2003.
- [17] Phenol Explorer INRA.
- [18] ANSES - Table de composition nutritionnelle des aliments - piments (Ciqual).
- [19] DJ Bennett and GW Kirby (1968) Constitution and biosynthesis of capsaicin. Journal of Chemical Society, 442-446.
- [20] Lee Y., Howard L. R., Villalon B. (1995) Flavonoids and antioxidant activity of fresh pepper (*Capsicum annuum*) cultivars. Journal of Food Science 60: 473-476.
- [21] Howard L. R., Talcott S. T., Brenes C. H., Villalon B. (2000) “Changes in phytochemical and antioxidant activity of selected pepper cultivars (*Capsicum* species) as influenced by maturity”. Journal of Agricultural and Food Chemistry 48: 1713-1720 PubMed (10820084).
- [22] Michael H. Davidson “Revue générale du métabolisme des lipides”, MD, FACC, FNLA, University of Chicagoo Medecine.
- [23] Jacques E. POISSON, «ALCALOÏDES», Encyclopædia Universalis.
- [24] J. B. Van Rijswijk, E. L. Boeke, J. M. Keizer, P. G. H. Mulder, H. M. Blom, W. J. Fokkens. Department of Otorhinolaryngology, Erasmus Medical Centre, Rotterdam, The Netherlands; Department of Epidemiology & Biostatistics, Erasmus Medical Centre, Rotterdam, The Netherlands; Department of Otorhinolaryngology and Head & Neck Surgery, The Red Cross Hospital and The Juliana Children Hospital, The Hague, The Netherlands dans Allergy 58 (8), 754-761.
- [25] Marvin P. Fried, MD, Montefiore Medical Center, The University Hospital of Albert Einstein College of Medicine. “Rhinite non allergique”.
- [26] Nicola L. Jones, Souheil Shabaib, Philip M. Sherman «Capsaicin as an inhibitor of the growth of the gastric pathogen *Helicobacter pylori*» Elsevier – FEMS MICROBIOLOGY LETTERS 146 (1997) 223-227 – Division of Gastroenterology and Nutrition Research, The Hospital for Sick Children Departments of Pediatrics and Microbiology University of Toronto, Ont M5G 1X8 Canada – Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.
- [27] Nimish Vakil, MD, University of Wisconsin School of Medicine and Public Health Dernière révision totale mars 2020| Dernière modification du contenu mars 2020. ” Infection à *Helicobacter pylori*”.
- [28] Ágata Ramos-Torres, Alicia Bort, Cecilia Morell, Nieves Rodríguez-Henche, and Inés Díaz-Laviada: “The pepper's natural ingredient capsaicin induces autophagy blockage in prostate cancer cells” Department of System Biology, Biochemistry and Molecular Biology Unit, School of Medicine, Alcalá University, Alcalá de Henares 28871, Madrid, Spain 2016 Jan 12; 7 (2): 1569-83. doi: 10.18632/oncotarget.6415.
- [29] Kannan, Muthukumar; Riekhof, Wayne R.; Voelker, Dennis R. (2015). "Transport of Phosphatidylserine from the Endoplasmic Reticulum to the Site of Phosphatidylserine Decarboxylase2 in Yeast". Traffic. 16 (2): 123–134. doi: 10.1111/tra.12236. ISSN 1600-0854. PMID 25355612.
- [30] <https://fr.wikipedia.org/wiki/Phosphatidylsérine>
- [31] Catherine Sarazin LIS2 Biochimie 2016 - Structure Des Protides: Acides Aminés, Peptides, Protéines.
- [32] Camille Lefebvre, Léa Zubiria «La sérine: Tout sur cet acide aminé» - passeportsanté – Octobre 2017 – Juin 2018.
- [33] Ohlrogge JB, Jaworski JG (June 1997). "Regulation of fatty acid synthesis". Annual Review of Plant Physiology and Plant Molecular Biology. 48: 109–136. doi: 10.1146/annurev.arplant.48.1.109. PMID 15012259. S2CID 46348092.
- [34] «ZOSTRIX® - AFT pharmaceuticals».
- [35] Saebyeol Jang, Keith W. Kelley, Rodney W. Johnson. “Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1”. Proc Natl Acad Sci U S A. 2008 May 27; 105 (21): 7534–7539.
- [36] Dong, X.; Wang, Y.; Liu, T.; Wu, P.; Gao, J.; Xu, J.; Yang, B.; Hu, Y. “Flavonoids as Vasorelaxant Agents: Synthesis, Biological Evaluation and Quantitative Structure Activities Relationship (QSAR) Studies”. Molecules 2011, 16, 8257-8272.

- [37] Ko WG, Kang TH, Lee SJ, Kim YC, Lee BH. "Effects of luteolin on the inhibition of proliferation and induction of apoptosis in human myeloid leukaemia cells". *Phytother Res.* 2002 May; 16 (3): 295-8. PMID 12164283.
- [38] Shin, Soon Young & Yong, Yeonjoong & Hong, Dae & Lee, Da & Lee, Da & Lee, Young. (2015). "Identification of flavonoids from *Eriodictyon californicum* and their cytotoxicity against HCT116 colon cancer cells". *Journal of the Korean Society for Applied Biological Chemistry.* 58. 10.1007/s13765-015-0015-0.
- [39] Eddouks Mohamed, Chattopadhyay Debprasad. "Phytotherapy in the Management of Diabetes and Hypertension". Bentham Science Publishers, 2012. eISBN: 978-1-60805-014-7.
- [40] Emran TB, Rahman MA, Uddin MMN, et al. "Molecular docking and inhibition studies on the interactions of *Bacopa monnieri*'s potent phytochemicals against pathogenic *Staphylococcus aureus*". *DARU Journal of Pharmaceutical Sciences.* 2015; 23 (1): 26. doi: 10.1186/s40199-015-0106-9. PMID 25884228.
- [41] Agnes W. Boots, Guido R. M. M. Haenen et Aalt Bast, «Health effects of quercetin: From antioxidant to nutraceutical», *European Journal of Pharmacology*, vol. 585, nos 2-3, 2008 <https://fr.wikipedia.org/wiki/Quercétine>
- [42] Andreas Kampkötter, Claudia Timpel, Ruben Felix Zurawski, Sven Ruhl, Yvonne Chovolou, Peter Proksch et Wim Wätjen, «Increase of stress resistance and lifespan of *Caenorhabditis elegans* by quercetin», *Comparative Biochemistry and Physiology*, vol. 149, 2008, p. 314-323.
- [43] Akira Murakami, Hitoshi Ashida et Junji Terao, «Multitargeted cancer prevention by quercetin», *Cancer Letters*, vol. 269, 2008.
- [44] R. L. Edwards, T. Lyon, S. E. Litwin, A. Rabovsky, J. D. Symons et T. Jalili, «Quercetin reduces blood pressure in hypertensive subjects» *J. Nutr.*, vol. 137, 2007.
- [45] A. W. Boots, M. Drent, V. C. J. de Boer, A. Bast et G. R. M. M., Haenen, «Quercetin reduces markers of oxidative stress and inflammation in sarcoidosis», submitted for publication, 2003.
- [46] DA Shoskes, SI Zeitlin, A Shaded et J Rajfer, «Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial», *Urology*, vol. 54, no 6, 1999.
- [47] Madhavan P Nair, Supriya Mahajan, Jessica L Reynolds, Ravikumar Aalinkeel, Harikrishnan Nair, Stanley A Schwartz, Chithan Kandaswami "The flavonoid quercetin inhibits proinflammatory cytokine (tumor necrosis factor alpha) gene expression in normal peripheral blood mononuclear cells via modulation of the NF-kappa beta system" *Clinical and Vaccine Immunology.* 2006 Mar; 13 (3): 319-28. doi: 10.1128/CVI.13.3.319-328.2006. Department of Medicine and Microbiology, Kaleida Health System, Buffalo General Hospital, State University of New York at Buffalo, Buffalo, NY 14203, USA. [mnair@acsu.buffalo.edu](mailto:mnair@acsu.buffalo.edu)
- [48] Walter Swardfager, Krista Lanctôt, Lana Rothenburg, Amy Wong, Jaclyn Cappell, Nathan Herrmann - "A meta-analysis of cytokines in Alzheimer's disease" *Biological Psychiatry.* 2010 Nov 15; 68 (10): 930-41. doi: 10.1016/j.biopsych.2010.06.012. Epub 2010 Aug 8. Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada.
- [49] R M Locksley, N Killeen, M J Lenardo - "The TNF and TNF receptor superfamilies: integrating mammalian biology" *Cell.* 2001 Feb 23; 104 (4): 487-501. doi: 10.1016/S0092-8674(01)00237-9. Department of Medicine, University of California, San Francisco, San Francisco, CA 94143, USA. [locksley@medicine.ucsf.edu](mailto:locksley@medicine.ucsf.edu)
- [50] Yekta Dowlati 1, Nathan Herrmann, Walter Swardfager, Helena Liu, Lauren Sham, Elyse K Reim, Krista L Lanctôt - "A meta-analysis of cytokines in major depression" *Biological Psychiatry.* 2010 Mar 1; 67 (5): 446-57. doi: 10.1016/j.biopsych.2009.09.033. Epub 2009 Dec 16. Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada.
- [51] Haiming Chen, Chuanjian Lu, Huazhen Liu, Maojie Wang, Hui Zhao, Yuhong Yan, Ling Han - "Quercetin ameliorates imiquimod-induced psoriasis-like skin inflammation in mice via the NF-κB pathway" *Elsevier International Immunopharmacology Volume 48, July 2017, Pages 110-117* <https://doi.org/10.1016/j.intimp.2017.04.022> Second Affiliated Hospital, Guangzhou University of Chinese Medicine, Guangzhou 510115, PR China; Postdoctoral Programme, Guangzhou University of Chinese Medicine, Guangzhou 510006, PR China; Guangdong Provincial Hospital of Chinese Medicine, Guangzhou 510115, PR China; Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou 510006, PR China.
- [52] Solomon Habtemariam, Abebech Belai - "Natural Therapies of the Inflammatory Bowel Disease: The Case of Rutin and its Aglycone, Quercetin" *Mini Reviews In Medicinal Chemistry* - doi: 10.2174/1389557517666170120152417. Pharmacognosy Research Laboratories & Herbal Analysis Services, Chatham-Maritime, Kent ME4 4TB, United Kingdom. - Enteric Neuroscience Lab, Health Sciences Research Centre, Department of Life Sciences, University of Roehampton London, Whitelands College, Holybourne Avenue, London SW15 4JD, United Kingdom.
- [53] R K Oldham - "Natural killer cells: artifact to reality: an odyssey in biology" *Cancer metastasis review* - 1983; 2 (4): 323-36. doi: 10.1007/BF00048565.
- [54] David Ermert, Maria J Niemiec, Marc Röhm, Andreas Glenthøj, Niels Borregaard, Constantin F Urban - "Candida albicans escapes from mouse neutrophils" *Journal of leukocyte biology* - 2013 Aug; 94 (2): 223-36. doi: 10.1189/jlb.0213063. Epub 2013 May 6. Laboratory for Molecular Infection Medicine Sweden, Umeå Centre for Microbial Research, Umeå University, Sjukhusområdet 6C, 90185 Umeå, Sweden.
- [55] V Witko-Sarsat, P Rieu, B Descamps-Latscha, P Lesavre, L Halbwachs-Mecarelli - "Neutrophils: molecules, functions and pathophysiological aspects" *Laboratory investigation a journal of technical methods and pathology.* 2000 May; 80 (5): 617-53. doi: 10.1038/labinvest.3780067. INSERM U507, Necker Hospital, Paris, France. [witko-sarsat@necker.fr](mailto:witko-sarsat@necker.fr)
- [56] R. Clark, S. Klebanoff - "The neutrophil: Function and clinical disorders" *Corpus ID: 82086000* Published 1978 *Medicine.*
- [57] Carl Nathan - "Neutrophils and immunity: challenges and opportunities" *Nature Review Immunology.* 2006 Mar; 6 (3): 173-82. doi: 10.1038/nri1785. Department of Microbiology and Immunology, Weill Cornell Medical College, Weill Graduate School of Medical Sciences of Cornell University, Box 57, 1300 York Avenue, New York 10021, USA. [cnathan@med.cornell.edu](mailto:cnathan@med.cornell.edu)
- [58] Paul Ehrlich - "Beiträge für Theorie und Praxis der histologischen Färbung" Leipzig, 1878.

- [59] Elaine Zayas Marcelino da Silva, Maria Célia Jamur, Constance Oliver – “Mast cell function: a new vision of an old cell” *The journal of histochemistry and cytochemistry: official journal of the histochemistry society* 2014 Oct; 62 (10): 698-738. doi: 10.1369/0022155414545334. Epub 2014 Jul 25. Department of Cell and Molecular Biology and Pathogenic Bioagents, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil (EZMDS, MCJ, CO) coliver@fmrp.usp.br
- [60] Stavros Polyzoidis, Triantafyllia Koletsis, Smaro Panagiotidou, Keyoumars Ashkan, and Theoharis C. Theoharidescorresponding author – “Mast cells in meningiomas and brain inflammation” *Journal of neuroinflammation* 2015; 12: 170. Published online 2015 Sep 17. doi: 10.1186/s12974-015-0388-3.
- [61] Jinmin Lee, Sarah L. Veatch, Barbara Baird, and David Holowka – “Molecular mechanisms of spontaneous and directed mast cell motility” *Journal of leukocyte biology* 2012 Nov; 92 (5): 1029–1041. doi: 10.1189/jlb.0212091.
- [62] Borros Armeth – “Gut-brain axis biochemical signalling from the gastrointestinal tract to the central nervous system: gut dysbiosis and altered brain function” *Postgraduate medical journal* - 2018 Aug; 94 (1114): 446-452. doi: 10.1136/postgradmedj-2017-135424. Epub 2018 Jul 19. Justus-Liebig-Universität Gießen.
- [63] Jacek Budzyński, Maria Kłopocka – “Brain-gut axis in the pathogenesis of *Helicobacter pylori* infection” *World J Gastroenterol* 2014 May 14; 20 (18): 5212-25. doi: 10.3748/wjg.v20.i18.5212. Jacek Budzyński, Department of Gastroenterology, Vascular Diseases and Internal Medicine, Nicolaus Copernicus University, The Ludwik Rydygier Collegium Medicum in Bydgoszcz, 85-168 Bydgoszcz, Poland.
- [64] Marilia Carabotti, Annunziata Scirocco, Maria Antonietta Maselli, and Carola Severia – “The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems” *Ann Gastroenterol.* 2015 Apr-Jun; 28 (2): 203–209. PMID: PMC4367209 - PMID: 25830558.
- [65] <https://psychscenehub.com/psychinsights/the-simplified-guide-to-the-gut-brain-axis/>
- [66] Antonina A Mikocka-Walus, Deborah A Turnbull, Nicole T Moulding, Ian G Wilson, Jane M Andrews, Gerald J Holtmann – “Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: a literature review” *Inflammatory bowel diseases* 2007 Feb; 13 (2): 225-34. doi: 10.1002/ibd.20062. School of Psychology, University of Adelaide, Adelaide, SA, Australia. antonina.mikockawalus@adelaide.edu.au
- [67] Kinga Bobińska, Elżbieta Gałęcka, Janusz Szemraj, Piotr Gałęcki, Monika Talarowska – “Is there a link between TNF gene expression and cognitive deficits in depression?” *Acta biochimica polonica* 2017; 64 (1): 65-73. doi: 10.18388/abp.2016\_1276. Epub 2016 Dec 16. Department of Adult Psychiatry, Medical University of Lodz, Łódź, Poland - Department of Pulmonology and Allergology, Medical University of Lodz, Łódź, Poland - Department of Medical Biochemistry, Medical University of Lodz, Łódź, Poland.
- [68] Epithelium Meaning in the Cambridge English Dictionary. [dictionary.cambridge.org](http://dictionary.cambridge.org)
- [69] Eurell, Jo Ann C.; et al., eds. (2006). *Dellmann's textbook of veterinary histology*. Wiley-Blackwell. p. 18. ISBN 978-0-7817-4148-4.
- [70] Mitchell, Richard Sheppard; Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson (2007) - "Ch. 13: Box on morphology of squamous cell carcinoma". *Robbins Basic Pathology* (8th ed.). Philadelphia: Saunders. ISBN 978-1-4160-2973-1.
- [71] Alberts B, Johnson A, Lewis J, et al. – “Molecular Biology of the Cell. 4th edition.” - New York: Garland Science; 2002.
- [72] Daniel P. Kaufman; Terrence Sanvictores; Michael Costanza – “Weibel Palade Bodies” SUNY Upstate Medical University, Touro University, Nevada, State University of NY Upstate.
- [73] Kalagara T, Moutsis T, Yang Y, Pappelbaum KI, Farken A, Cladder-Micus L, Vidal-Y-Sy S, John A, Bauer AT, Moerschbacher BM, Schneider SW, Gorzelanny C. “The endothelial glycocalyx anchors von Willebrand factor fibers to the vascular endothelium”. *Blood Adv.* 2018 Sep 25; 2 (18): 2347-2357.
- [74] Nicholas R., KunioMD, Martin A., SchreiberMD “Topical Hemostatic Agents” - Consultative Hemostasis and Thrombosis (Third Edition) - Expert Consult - Online and Print - 2013, Pages 538-545 – Elsevier.
- [75] Jorge Escribano, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing, Michelle B. Chen, Conceptualization, Data curation, Investigation, Writing – review & editing, Emad Moendarbary, Data curation, Validation, Writing – review & editing, Xuan Cao, Methodology, Writing – review & editing, Vivek Shenoy, Methodology, Writing – review & editing, Jose Manuel Garcia-Aznar, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing, \*Roger D. Kamm, Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing\* and Fabian Spill, Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing \*Andrew D. McCulloch, Editor – “Balance of mechanical forces drives endothelial gap formation and may facilitate cancer and immune-cell extravasation” - *PLoS Comput Biol.* 2019 May; 15 (5): e1006395. Published online 2019 May 2. doi: 10.1371/journal.pcbi.1006395 Department of Mechanical Engineering, University of Zaragoza, Zaragoza, Spain, Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America, Department of Bioengineering, Stanford University, Stanford, California, United States of America, Department of Mechanical Engineering, University College London, London, United Kingdom, Department of Materials Science and Engineering, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America, Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America, BioSystems and Micromechanics (BioSyM), Singapore-MIT Alliance for Research and Technology, Singapore, Singapore, School of Mathematics, University of Birmingham, Birmingham, United Kingdom, University of California San Diego, United States.
- [76] M Iantorno, U Campia, N Di Daniele, S Nistico, G B Forleo, C Cardillo, M Tesaro – “Obesity, inflammation and endothelial dysfunction” *J Biol Regul Homeost Agents.* Apr-Jun 2014; 28 (2): 169-76. PMID: 25001649.
- [77] Martin K Reriani, Lilach O Lerman, and Amir Lerman – “Endothelial function as a functional expression of cardiovascular risk factors” *Biomark Med.* 2010 Jun; 4 (3): 351–360. doi: 10.2217/bmm.10.61.

- [78] G J Blake, P M Ridker – “Inflammatory bio-markers and cardiovascular risk prediction” *Journal of Internal medicine* - 2002 Oct; 252 (4): 283-94. doi: 10.1046/j.1365-2796.2002.01019.x. Center for Cardiovascular Disease Prevention and the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue East, Boston, MA 02215, USA.
- [79] Yoshiko Mizuno, Robert Francis Jacob, R Preston Mason – “Inflammation and the development of atherosclerosis” *Journal of atherosclerosis and thrombosis* 2011; 18 (5): 351-8. doi: 10.5551/jat.7591. Epub 2011 Mar 18. Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Japan.
- [80] Esther Lopez-Garcia, Frank B Hu – “Nutrition and the endothelium” *current diabetes report* - 2004 Aug; 4 (4): 253-9. doi: 10.1007/s11892-004-0076-7. Department of Nutrition, Harvard School of Public Health and Channing Laboratory, 665 Huntington Avenue, Boston, MA 02115, USA. elopezga@hsph.harvard.edu
- [81] Mikko I Mäyränpää, Hanna M Heikkilä, Ken A Lindstedt, Andrew F Walls, Petri T Kovanen – “Desquamation of human coronary artery endothelium by human mast cell proteases: implications for plaque erosion” *coronary artery disease* - 2006 Nov; 17 (7): 611-21. doi: 10.1097/01.mca.0000224420.67304.4d. Wihuri Research Institute, University of Helsinki, Helsinki, Finland.
- [82] Lars Lind - “Circulating markers of inflammation and atherosclerosis” - *Atherosclerosis*. 2003 Aug; 169 (2): 203-14. doi: 10.1016/s0021-9150(03)00012-1.
- [83] A B Thompson, R A Robbins, D J Romberger, J H Sisson, J R Spurzem, H Teschler, S I Rennard – “Immunological functions of the pulmonary epithelium” *The European respiratory journal* - 1995 Jan; 8 (1): 127-49. doi: 10.1183/09031936.95.08010127. Dept of Internal Medicine, University of Nebraska Medical Center, Omaha 68198-5300, USA.
- [84] V Godding, J M Stark, J B Sedgwick, W W Busse – “Adhesion of activated eosinophils to respiratory epithelial cells is enhanced by tumor necrosis factor-alpha and interleukin-1 beta” *American journal of respiratory cell and molecular biology* - 1995 Nov; 13 (5): 555-62. doi: 10.1165/ajrcmb.13.5.7576691. UCL Mont-Godinne and Experimental Medicine Unit (ICP), Catholic University of Louvain, Belgium.
- [85] J M Stark, V Godding, J B Sedgwick, W W Busse – “Respiratory syncytial virus infection enhances neutrophil and eosinophil adhesion to cultured respiratory epithelial cells. Roles of CD18 and intercellular adhesion molecule-1” *Journal of immunology (Baltimore Md-1950)* - 1996 Jun 15; 156 (12): 4774-82. Pulmonary Medicine, Department of Pediatrics, Children's Hospital Medical Center, Cincinnati, OH, USA.
- [86] Maurizio Marini MD, Enza Vittori PhD, Jan Holleborg PhD, Sabrina Mattoli MD, PhD – “Expression of the potent inflammatory cytokines, granulocyte-macrophage-colony-stimulating factor and interleukin-6 and interleukin-8, in bronchial epithelial cells of patients with asthma” *Journal of Allergy and Clinical Immunology* Volume 89, Issue 5, May 1992, Pages 1001-1009.
- [87] G D Martich, R L Danner, M Ceska, A F Suffredini – “Detection of interleukin 8 and tumor necrosis factor in normal humans after intravenous endotoxin: the effect of antiinflammatory agents” *The journal of experimental medicine* - 1991 Apr 1; 173 (4): 1021-4. doi: 10.1084/jem.173.4.1021. Critical Care Medicine Department, National Institutes of Health, Bethesda, Maryland 20892.
- [88] Murray RF, Harper HW, Granner DK, Mayes PA, Rodwell VW (2006). *Harper's Illustrated Biochemistry*. New York: Lange Medical Books/McGraw-Hill. ISBN 978-0-07-146197-9.