Medica and Clinica Press

Publishing press
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Review

Nutritional pharmacology – and beyond

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Received: *March 8th, 2017*
Accepted: *March 28th, 2017*
Published: *April 4th, 2017*

Citation
Télessy IG. Nutritional pharmacology – and beyond. *Med Clin Press*. 2017; 1(1): 12-19. doi: 10.28964/MedClinPress-1-103

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SUMMARY

Artificial nutrition became in the last decades very sophysticated. Today in most patient receive medical nutrition via oral (ONS) or enteral tube feeding, or parenteral nutrition (PN, mainly in form of multichamber bags), that contain macronutrients (aminoacids, carbohydrates and fats) as well as micronutrients (electrolytes, vitamins and trace elements). The latter will – in case of PN – usually be given just before infusion into the mixture of main components in an individualized dose. However, now-a-days we are able to identify pharmacological action of certain nutrients, as we have learned and searched continuously ingredients, that are not only energy-holders or protein-precursors but even have pharmacologically defined action. This action is usually dependent on dose and chemical structure. After pharmacological experiments clinical studies supported the benefits, e.g., antiinflammatory action of glutamine or n-3 fatty acids (with very different mechanism of action, of course). The present article displays by means of examples the switchback road of new pharmaconutrients from laboratory to hospital ward.

KEY WORDS: Oral nutrition support (ONS); Parenteral nutrition (PN); Glutamate; Omega-3 fatty acids; Pharmaconutrients.

Abbreviations: ONS: Oral nutrition support; PN: Parenteral nutrition; BCAA: Branched-chain amino acid; mTOR: mammalian target of rapamycin; mRNA: messenger ribonucleinic acid; GLN: Glutamine; GLU: Glutamate; CNS: Central Nervous System; ICU: Intensive Care Unit; FA: Fatty Acid; MUFA: Monounsaturated fatty acid; PUFA: Polyunsaturated fatt acid; TC: Total Cholesterol; LDL-C: Low density lipoprotein cholesterol, LCT-MCT: Long-chain triglyceride – medium-chain triglyceride; PNALD: Parenteral nutrition-associated liver disease.

INTRODUCTION

Medicine is a substance taken into the body for preventing or treating an illness. First medicines were herbs found in the field, later on main ingredients were extracted from herbs and used in concentrated form. In the synthetic era molecules having similar structure to natural substances but more potent than that of herbal origin were designed. Now-a-days more and more ingredients of foodstuff are identified as pharmacologically active substances. It means, biologically active ingredients that affect health in a dose-dependent manner, are subject of pharmacological evaluation in order to discover their potential to treat or prevent diseases. In this context many substances can act as remedies, but for being registered medicine they must be standardized and evaluated for safety, efficiency and effectiveness. The goal of this article serves to highlight how simple nutrient components developed from basic research to successful clinical use.

DEFINITIONS AND GENERAL CONSIDERATIONS

In the field of nutrition there are a lot of controversies and misunderstandings as terminology

is not uniform. ESPEN recently gave guideline for terminology,[1] however many frequently used terms and denominations are missing. Towards distinct understanding of nutritional pharmacology and pharmaconutrition some of them are elucidated as follows:

Nutritional pharmacology: means the pharmacological research of and knowlegde on substances coming from the field of nutrition. A lot of active ingredients of nutrients can specifically improve or repair an existing pathophysiological condition. Important to note that from pharmacological point of view active ingredients are effective and safe only if they were applied for the proper person (= accepted indication), if they were used in a well defined dose or dose-range that reaches the target organ (receptor) in an expected concentration and, if the duration of use was long enough to exert action. To make pharmaceuticals from certain substance, must be administered in a mode (form) that has been successfully tested from bioavailability point of view. In our days there are different aminoacids, fatty acids, nucleotids, endogenous microbes, special carbohydrates, etc. that can be used as pharmacologically active nutrient-components, and the results of research in this field are exponentially grow.

Furthermore there are different denominations for the curative use of nutrients and nutrient ingredients, that are sometimes confusing. These are the followings:

Clinical nutrition: means only that nutrients are used for support of undernourished people having increased risk of illnesses. Undernutrition from category point of view can be mixed undernutrition (deficit in macro- and micro-nutrients) or specific macro- or micronutrient deficit as well. In this context clinical nutrition is a protective intervention.

Nutrition therapy: means use of specific nutrients and foodstuffs for sick patients who already became ill due to incorrect under- or overnutrition or adverse eating behaviour. For undernourishment typical examples are pre- or post-operative patients with depleted nutrient stores, consequently with improper metabolic processes and defense mechanisms. Therefore, proper supplementation of missing nutrients is needed.

Pharmaconutrition: means treatment of patients with nutrients having a main ingredient or specific nutrient components with known pharmacological action in order to repair pathological conditions. This pharmacological action can be nutiritve and non-nutritive action as well. In case of pharmacotherapeutic use a dose-dependent action is expected and known mechanism of action helps in finding the best indications and efficiency. Within pharmaconutrition a specific group is formed by compounds exerting immunological action, which is typically non-nutritive action. Therapy made by these nutrients is referred as immunonutrition.[2] Denomination of pharmaconutrition appeared just after introduction of term immunonutrition,[3] therefore sometimes immunonutrition is used even if substrates are in broader sense discussed.

DEVELOPMENT OF PHARMACONUTRITION

Non-nutritive pharmaconutrition started as “off-label” use of nutrition therapy. Based on laboratory results or theoretical pharmacological considerations, some nutrient components that could enhance patients immun-reaction (e.g., arginine) were used in non-nutritive indication. After initial success, more and more nutrients became tool of such exeriments. However, one should see the controversies of fast emerging, not always evidence-based results as well. With classical pharmaceuticals we realized the phase of overestimation, followed by underestimation, finally the realistic evaluation of new chemical entities. The figure is similar in case of pharmaconutrients, too. After a decade of increasingly positive evaluation of pharmaconutrition (incl. immunonutrition)[4] and successfull development and launch of new products in the armamentarium of artificial nutrients, some autors are talking about end of era of pharmaconutrition.[5] However even today prosperous research activity is to be seen for finding more and more potent pharmaconutrients.[6,7]

Nutritive pharmaconutrients were invented much earlier than non-nutritives. First nutritive type pharmaconutrients were vitamins. Scientist realized the dose-dependent actions of vitamine-components of foodstufs and used in pharmacological/therapeutical dose in case of shortage of them in the organism. Later on, based on the relative atoxic feature of most vitamines, multivitamin products became “life-style consumer goods”. There were decades when vitamins and multivitamins were higher ranked than vegetables and fruits containing the natural vitamines. Today – inspite of advertisements of manufacturers and suppliers – more and more members of the society turns back to food of natural sources and the specific vitamin-preparations (mainly pharmaceuticals with reliable content and bioavailability) remains for the treatment of vitamin-deficits.

Third type of pharmaconutrients are the transients. The example is some of the aminoacids: in the eighties branched-chain aminoacids (BCAAs) were favorized in treatment of hepatic diseases, because we belived that by this intervention one can avoid or diminish endogenous production of false neurotransmitters and shortened results of hepatic encephalopathy.[8] Some a decade latert it became clear that hepatic encephalopathy is rather of multicausal orgin and by enrichment of parenteral nutrition solutions with BCAA one can hardly influence progress of this illness.[9] But today, due to the nutrient-centered pharmacological research, we know that minimally one of the BCAAs, the leucine, really plays an important role in the pharmaconutrition, by improving muscle protein synthesis (e.g., in treatment of sarcopenic patients). Leucine, however, (in presence of other BCAAs and essential amino acids) can stimulate mTOR signaling consequently increase the rate of mRNA translation and finally strenghen protein synthesis in patient with negative protein balance.[10] And in clinical studies this effect has been supported, too.[11,12]

The shift from pure nutrition-ingredient to pharmaconutrient is running today, too. Let’s take lycopene, for instance. Lycopene

is bioactive ingredient of eg. tomato that was discovered in the fifties. Potential role of lycopene for human health was published in 1997 at first.[13] In the same year an international symposium has been devoted to the first experiences in disease prevention.[14] And the mapping of pharmacological mechanisms of action by nutritional pharmacology started more than twenty years ago. The results come slowly because today much more aspects are to be cleared than some decades ago. And even if some lycopene-based pharmaceuticals are already registered and plenty of food supplements are sold, basic research and clinical studies are stil running as well as systematic reviews of studies are produced.[6,15,16]

Substrates used in the frame of pharmaconutrition are very different of origin and structure. Most often mentioned substrates are aminoacids and fatty acids because most thoroughly searched field of pharmacologically active nutrient ingredients are of these family of compounds. The most highlighted representatives of the above mentioned groups are glutamine and omega-3 fatty acids. Their story demonstrate the road of development of pharmaconutrient-candidates very spectacularly.

THE GLUTAMINE STORY

In clinical nutrition practice aminoacids – more precisely: aminoacid-mixtures – are administered in order to provide „bricks" to build up proteins which were lost due to catabolic and hypercatabolic processes. But aminoacids are not only units for building up proteins. They have much more physiological functions. This is well illustrated by various synthetic pathways in immuncells, where certain aminoacids with help of mTOR and protein-kinases can influence translation of mRNA and entire process of proteinsynthesis. Thus by provision of exogen aminoacids one can trigger pharmacological action.

Among aminoacids most pharmacological information is available about glutamine (GLN). Glutamine is a diamino-carbonic acid and glutamate (GLU) is monoamino-dicarbonic acid. Both molecules can convert to each-other by glutamin-synthase and glutaminase (Figure 1). Physiologically glutamine is not essential because it is synthetized from histidine and glutamate, moreover one metabolite of the citric acid cycle (alpha-ketoglutarate or 2-oxoglutarate) is also precursor of glutamine. GLN is, however also one of the main energy substrates, especially in the kidney, and participate in gluconeogenesis, mainly in the liver. All these show the multifunction (protein-producer and energy-source, too) of this molecule. In the circulation GLN is the most adundant aminoacid of all (e.g., 500-900 mol/L of glutamine *vs.* 50-70 mol/L of glutamate). Under certain circumstances (severe stress, sepsis, hypercatabolism, etc.) a glutamine efflux from muscle is tremendous and, fast catabolism can be demonstrated with decrease in GLN-level in the circulation as well as in the organs with a consequent metabolic insufficiency that increase the risk of patient for unfavourable outcome (Figure 2).

Reason is that circulating GLN is quickly utilised to energy and, within a very short periode of time GLN-deficit appears. Cut-off level in plasma is 420 mmol/L GLN.[17] Should GLN-supply disappeare, the systems collaps. This has been proved more than 20 years ago. In this situation glutamine supplementation (nutrition therapy) or therapeutic GLN-administration (pharmaconutrition) can be life saving intervention because different roles of GLN/GLU couple (energy-source, N-transporter and neurotransmitter functions) are continuously present.

From molecular pharmacological point of view GLN influence expression of genes responsible for metabolism, trasport and inflammation.[18] *In vitro* studies demonstrated that IL-2 output of lymphocytes and IL-1 production by macrophages depends on glutamine supply.[19] Glutamine support intracellular synthesis of acute-phase proteins.[20] GLN increases intracellular glutathion-concentration, so indirectly act antioxidant.[21] And improve the ammonia-production in the kidney, the excitatory neurotransmitter levels in CNS, precursors in the nucleotide synthesis, signaling molecule in tumor cells, etc. Moreover some of the other aminoacids are also concerned, e.g., the arginin which have various individual actions, too. As glutamine is precursor of ornithin, which converts to citrulline by the intestine. Citrulline transforms to arginine in the kidney.[22] So molecular interactions are also behind the final result.

Therefore it is difficult to demonstrate one specific mechanism with GLN, however improvement of metabolic network after glutamine-administration has been proven.

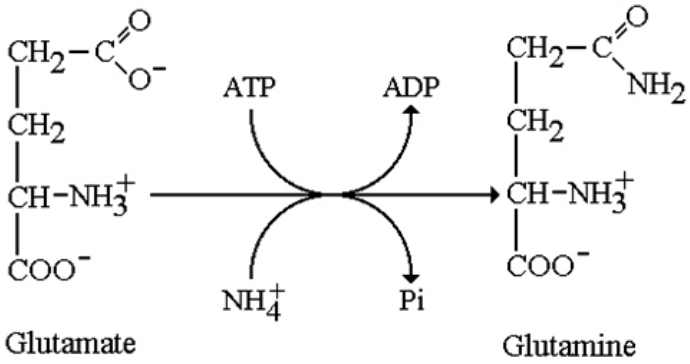

Figure 1: Glutamine-glutamate interconversion.

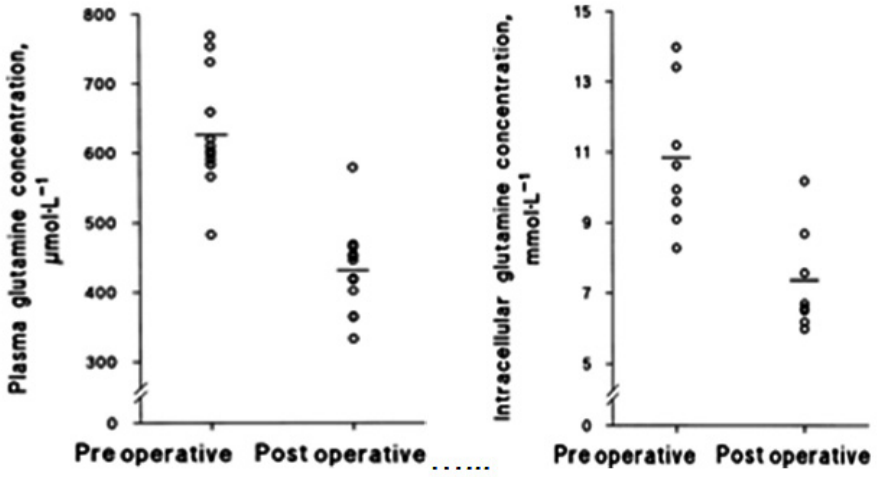

Figure 2: Decrease of plasma and intracellular glutamine concentrations after surgical stress.[31]

Some 5-10 years ago there was an extreme enthusiasm in use of glutamine. In most ICU wards and in many surgical and medical wards use of glutamine was a fashion. Many publications – unfortunately also poor ones from quality point of view – appeared pro and sometimes con. Later on, by 2011-2013 more criticism appeared about benefit of excesive and unreasonable glutamine administration and in 2013 Heyland and coworkers published that „…glutamine was associated with an increase in mortality…".[23] After this unexpected statement huge number of studies were re-evaluated and today we can see quite clear: the indications and the dosage of glutamine should be strictly kept. Here, like with all pharmaceuticals, indication as well as contraindications and dosage have very high impact. The point is that glutamine solution (in form of alanyl-glutamine [ALA-GLN] dipeptide because of instability of pure glutamine in watery solutions (Table 1) should be used only as additive to (mainly parenteral) nutrition, administration of pure glutamine-infusion is not allowed. The enteral route can be used for glutamine supplementation as well but bioavailability is much worse. Main therapeutic indications are various hipercatabolic states but severe renal or liver impairments and metabolic acidosis are contraindications. The ALA-GLN-dose should never be more than 0,5 mg/kgBW and must be calculate into the daily aminoacid-supply. In the above mentioned study (REDOX) neither contraindications nor dosage was accepted. In contraty to suggestions of REDOX study glutamine administration – when not supplemeted the just missing amount but given in therapeutic doses and to whom it really indicated – is safe and effective.[24]

The benefits in intensive care units that were realized by series of well designed studies after use of glutamine we can rate as very good: general decrease in mortality, in length of stay in hospitals, in infection rate (Figure 3) and in cost of care, too.

THE OMEGA-3 FATTY ACID STORY

Fats in nutrition therapy are mainly triacylglycerols. During their metabolism – after enzymatic cleavage – fatty acids (FAs) are deliberated from glyceride-bond and play an important role in energy-turnover as well as in many other biosynthetic pathways. Free fatty acids are incorporated into cellmembranes, too.

Aminoacis and dipeptides	Water solubilty (g/lit)	Stability
Cystine	0,1	Stable
Cysteine-HCl	252	Not stable
Bis-l-alanyl-l-cystine	> 500.0	Stable
Bis-glycyl-l-cystine	541	Stable
Tyrosine	0,4	Stable
l-Alanyl-l-tyrosine	14	Stable
Glycyl-l-tyrosine	30	Stable
Glutamine	36	Not stable
l-Alanyl-l-glutamine	568	Stable
Glycyl-l-glutamine	154	Stable

Table 1: Chemical characteristics of aminoacids and synthetic dipeptides.[32]

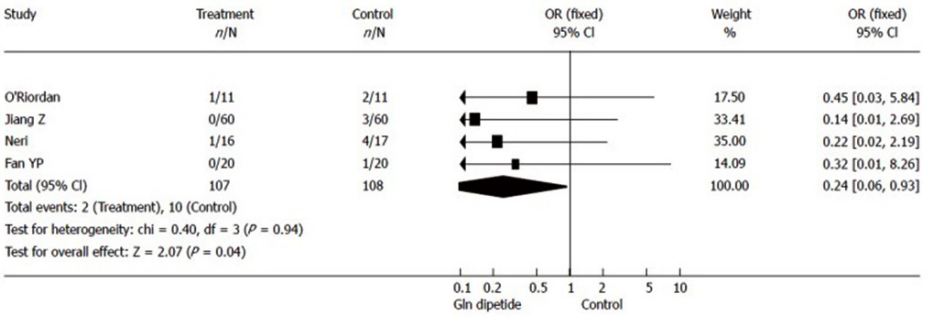

Figure 3: The decrease in occurence of infection due to use of glutamine taken over.[33]

Most consumed fats contain saturated and monounsturated fatty acids (MUFAs). Saturated FAs are unhealthy because they are mainly used for energy production or storage of energy and rise total cholesterol (TC) and LDL-cholesterol (LDL-C) in human being. Due to their physical inflexibility and lack of reactivity their participation in biosynthetic processes is poor. MUFAs are better from utilisation point of view, they lower TC and LDL-C level in human blood and decrease inflammatory triggers, however from metabolic point of view they are also mainly utilized as energy-source.

Poly-unsaturated fatty acids (PUFAs), due to their double bonds, are much more reactive and play an important role in synthesis of inflammatory mediators, actively participate in oxidative and antioxidative processes, in cellmembrane-flexibility and maybe in cancerogenesis. PUFAs consists of two main groups: the n-3 (e.g., alpha-linolenic acid, eicosapentaenic acid, docosahexaenic acid) and the n-6 fatty acids (mainly linoleic acid, arachidonic acid). If the former is incorporated into cell membranes and enriches intracellularly in higher proportion, it exerts immunmodulation and modulates receptor-expression, modifies lipid-protein bindings and – as main anti-inflammatory action – decreases synthesis of pro-inflammatory prostaglandins. Recently, lipid-lowering effect due to anti-inflammatory activity of n-3 fatty acids has been verified, too.[25] In contrast, n-6 fatty acids support synthesis of pro-inflammatory prostaglandines and other citokines. Therefore within PUFAs a special inpact is attributed to n-3 and n-6 fatty acid ratio in blood, in tissues and in cells. Their relation seems to be definitive in keeping homeostasis in the inflammatory/anti-inflammatory system. In optimal situation the n-3 : n-6 ratio should be between 1:2 and 1:3. The shift in this ratio – like deviation in eg. Na^+:K^+ ratio – results in pathological conditions (Figure 4).

Unfortunately, the ratio of n-3:n-6 in western diet is much worth than physiologically. Therefore the decrease of n-6 source and increase of n-3 FAs is desirable. Under clinical conditions, during artificial nutrition we have the opportunity to improve the

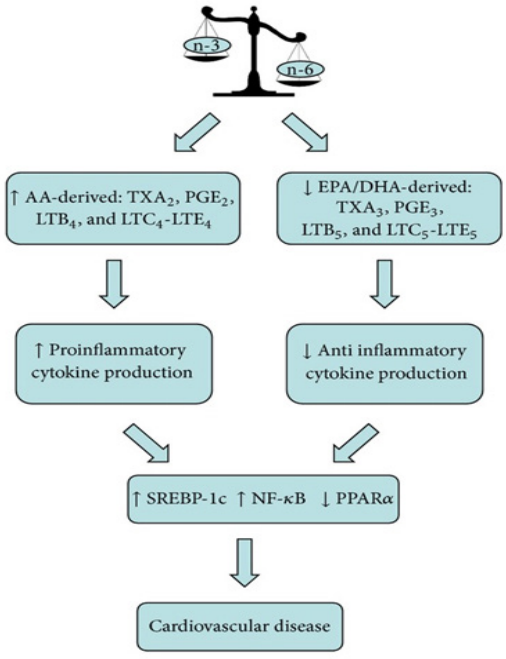

Figure 4: Consequences of deviation of ω-3 : ω-6 ratio.

ratio: today we have fish-oil containing lipid emulsion, that can help in short-term restitution of the n-3:n-6 ratio. By this intervention we can artificially influence cell-membrane functions and the synthesis of inflammatory/anti inflammatory mediators, consequently we can modify cellular reactions for the patients benefit.

The parenteral nutrition admixtures consist of macronutrients carbohydrates + aminoacids + fats. The fat component was for over 40 years dominantly soybean oil, which is in 60-70% n-6 FAs (n-6:n-3 ratio ca. 7:1). Recently the dominance of soybean oil only or soybean oil-coconut oil (LCT-MCT) combination turned to fat-mixtures containing higher and higher proportion of n-3 FAs, referred as to "third-generation" mixed lipid emulsions (n-6:n-3 ratio 2:1 – 3:1). In practice this means: we are able to decrease risk of eg. PNALD (parenteral nutrition associated inflammatory liver disease), we can diminish occurence of acute tissue inflammations associated with surgical interventions and the postoperative infections etc. (Figure 5). These examples demonstrate that by well defined doses of n-3 long chain fatty acids we are able to pharmacologically modify inflammatory processes and other metabolic or catabolic reactions.

DISCUSSION

Medical doctors and pharmacists working in the field of artificial nutrition, realized a substantial change in the nutritional therapy. Many new components arrived into the therapeutic palette and the option of individual therapy became plausible. The new compounds were coming from the field of daily foodstuff, and due to close cooperation of nutritionists and pharmacologists after thorough research activity became possible to verify pharmacological activity of some food ingredients. In the territory of macronutrients (amino acids[26] and fats[27]) or the micronutrients (vitamins, trace elements[28]) there were huge step forward and today medical professionals are able to provide patients with artificial nutrition with various therapeutic benefits. Development of pharmaconutrients offers various treatment modalities according to the pathophysiology of patients. However there are still challenges as the individual variations in characteristics of pathological situations are very rich. We have learned that pharmacological actions can be different in various illnesses and usually does not exist „one fit all" solution in this field. Therefore a lot of well designed, randomized, controlled, multicenter studies are needed to reach results that make safe the use of pharma-nutrients and are acceptable by the health authorities, too. Good example is the meta-analysis of n-3 polyunsaturated fatty acids used for treatment of cancer-patients: there are results in gastrointestinal cancer[29] and separately in colorectal cancer patients[30] but the final conclusions are not the same. And despite all these efforts we have seen treatment failures and unbelivable positive outcomes after use of new pharmaceutical candidates as well. However, today there is consensus about net proceeds of use of compounds that were not utilized some two or three decades ago, like fish oil or glutamine or arginine etc. under certain pathological conditions. And pharmaceuticals containing these new components substitute older compounds that were used for decades before: this is the proof of success.

CONCLUSIONS

Nutritional pharmacology should intensify the research activity. For the time being, we realized that we know quite much however not enough. Indications and dose-respons relations should be cleared much deeper then previously and clinical studies must be planned more carefully. Correct results can be reached only by well designed studies. Patients' metabolic and organ specific conditions must be cleared – as in case of use of high efficient classic pharmaceuticals – before use of pharmaconiutrients. Pharmaconutrition is an effective and in the same time smoth

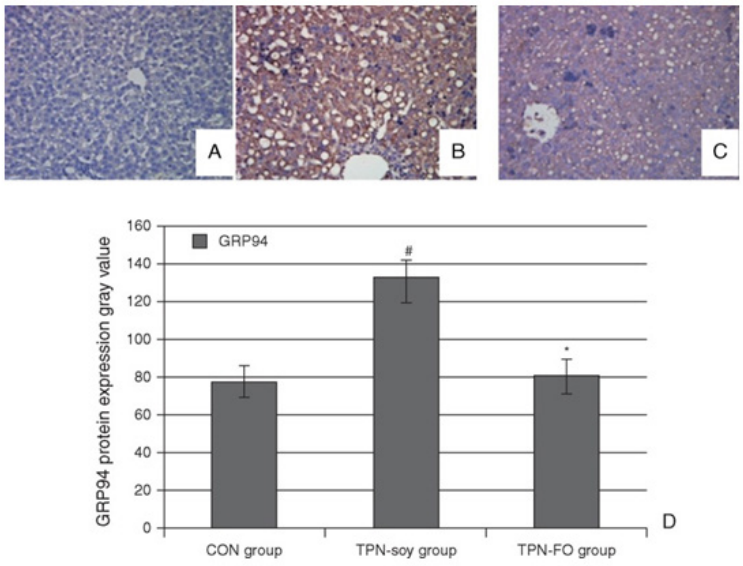

Figure 5: The effect of w-3 enriched parenteral lipid emulsion on development of PNALD.[34]

therapeutic mode. In this way of treatment one can use selected components of nutrients like evidence based pharmaceuticals. To reach this point thorough evaluation of therpeutic action of ingredients is necessary in order to learn details of mechanisms of action and find proper pharmacotherapeutic targets. Sometimes special pharmaceutical treatment with nutrient component is needed in ordet to get useful and safe tool for therapeutic intervention. By the pharmaconutrients we can reach huge development in therapeutic interventions.

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