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Comparison of Iron-Based Supplements and their Possible Use in Adjuvant Therapy in Oncology Patients

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ABSTRACT

The study of iron metabolism is one of the most widespread topics in medical literature, where it is treated with different approaches and methods and with different protocols. This depends on the particular chemical-physical properties of iron, which make it an element that is difficult to manage both as a chemical substance and as an element that, although physiologically essential, has limited therapeutic margins. In this study we discuss extensively the chemical aspects of iron, and the metabolic activities in which it participates as an essential biological element. Its necessity and diffusion in all fundamental biological processes, which we recall in this work, has stimulated the search for various forms of delivery and administration, which would make it more easily manageable.The aim of this article is to compare the various formulations and technologies with which it is proposed on the market, and in particular to present our original formulation that we have used in a particularly difficult to treat case history, such as that of cancer patients, as an adjuvant to basic chemotherapy. The positive results we have obtained in the small case study we present encourage us to continue the research with larger and more detailed case studies, and as an effective and safe aid, to be used in all cases of iron deficiency and anemia in all its expressions.

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Introduction

To understand the usefulness of iron (Fe) supplements in deficiency states, it is necessary to preliminarily know the chemical properties and also those of the trace elements that contribute to its metabolism and homeostasis.

Iron plays a fundamental role in numerous metabolic and synthetic processes, it is enough to remember the synthesis of heme and its essential participation in the respiratory chain, etc., despite this, the description of its metabolism is extremely complex and still not completely understood.

In this article we will give only a few hints of this essential biological process.

Iron is one of the most abundant chemical elements in nature and has particular chemical properties, deducible from its position in the periodic table of elements, Figure 1 which make it perfect for vital functions. In fact, we find it in all living organisms where it plays fundamental metabolic roles.

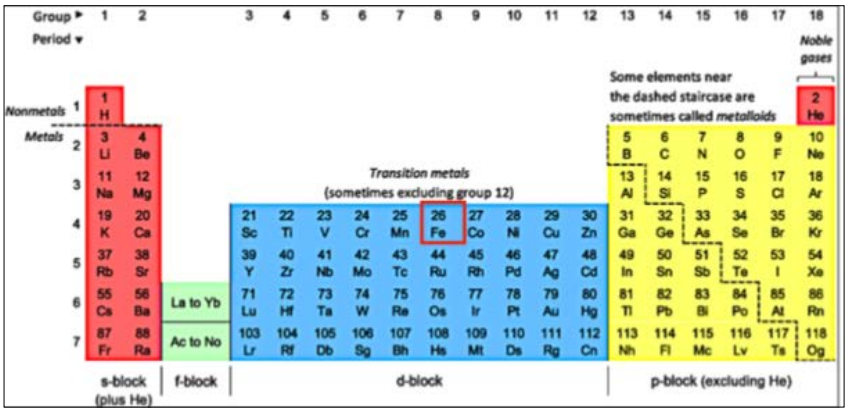


Figure 1: Position of Iron on the Periodic Table of Elements

It constitutes an important part of the rocks that form the Earth's crust and is believed to be present in the centre of the Earth where it forms the main component of the incandescent magmatic mass, and to have played a fundamental role in the origin of life [1]. Figure 2.

The Iron Cycle at the Origin of Life

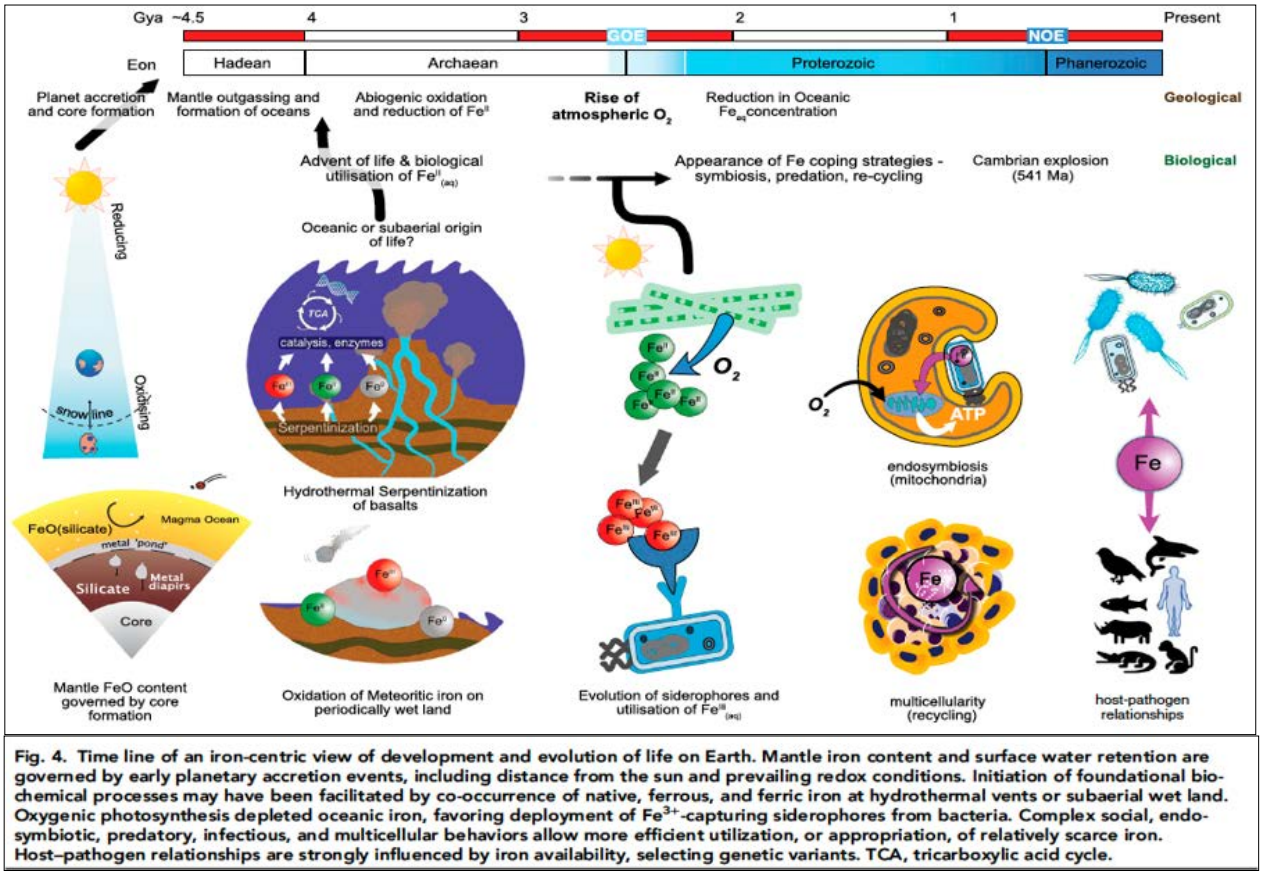


Fig. 4. Time line of an iron-centric view of development and evolution of life on Earth. Mantle iron content and surface water retention are governed by early planetary accretion events, including distance from the sun and prevailing redox conditions. Initiation of foundational biochemical processes may have been facilitated by co-occurrence of native, ferrous, and ferric iron at hydrothermal vents or subaerial wet land. Oxygenic photosynthesis depleted oceanic iron, favoring deployment of Fe^{3+}-capturing siderophores from bacteria. Complex social, endosymbiotic, predatory, infectious, and multicellular behaviors allow more efficient utilization, or appropriation, of relatively scarce iron. Host–pathogen relationships are strongly influenced by iron availability, selecting genetic variants. TCA, tricarboxylic acid cycle.

Figure 2: Schematic of the Hypothetical Participation of Iron in the Origin of Life

Iron is thought to have played a fundamental role both in the genesis of the planet Earth and in the formation and differentiation of the first ancestral aerobic organisms. At the origin of these organisms, it contributed to promoting the synthesis of agglomerates of oxidation-reducing macromolecules capable of transporting electrons to the terminal oxygen acceptor.

From these primitive agglomerates the respiratory chain originated in the first ancestral archaea, which were then absorbed by primitive single-celled biological forms to form mitochondria and chloroplasts Figure 3.

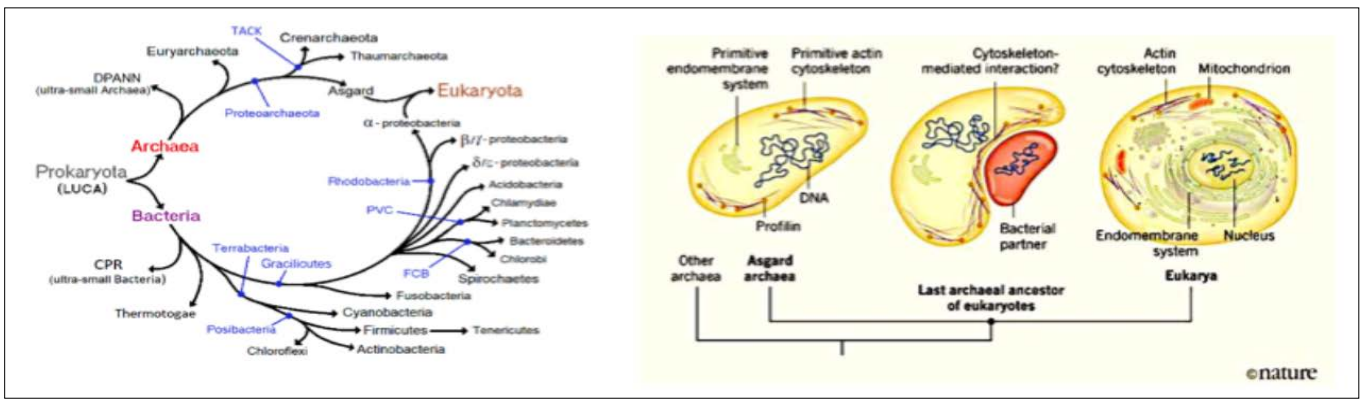
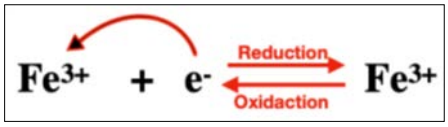


Figure 3: Contribution of Iron in the Evolution of Life

Chemical Properties of Iron

- Iron is a chemical element belongs to the group of transition metals
- Very reactive and can form complexes with other molecules present in solution.
- For this reason, iron in living organisms is always "tied" to other molecules which control it like a special surveillance.
- In aqueous solution, iron exists in two main forms of oxidation: ferrous (Fe++) and ferric (Fe+++). The passage from the oxidized state to the reduced state occurs very easily in biological systems this also explains the high toxicity of this element:



- Which if present in free ionic form in solution generates dangerous free radicals with high oxidizing power

Iron in its compounds occurs in two ionic forms or oxidation states:
Ferrous Iron: Fe 2+ and Ferric Iron: Fe 3+; In these states it performs three important functions in living beings: Functional Iron, Transport Iron and Reserve Iron Figure 4

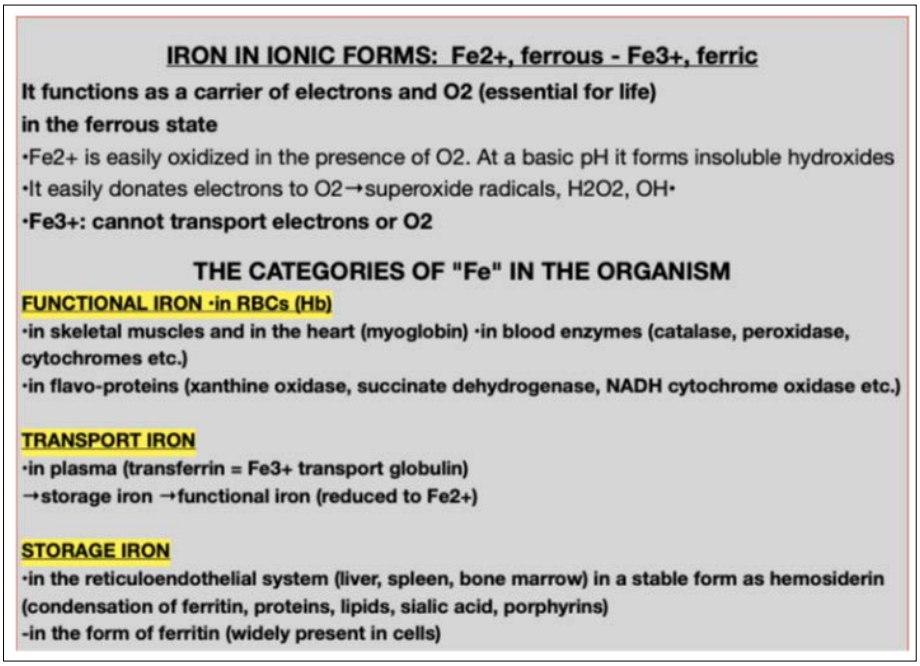


Figure 4: Main Categories of Iron Functions

This multiple and essential metabolic function explains why iron deficiency, among all trace element deficiencies, is the most widespread in the world population, according to the World Health Organization, WHO [2]:

- Anemia is major public health concern, mainly affecting young children, pregnant and postpartum women, and menstruating adolescent girls and women.
- Globally, it is estimated that 40% of all children aged 6–59 months, 37% of pregnant women and 30% of women 15–49 years of age are affected by anaemia.
- Anaemia caused 50 million years of healthy life lost due to disability in 2019. The largest causes were dietary iron deficiency, thalassaemia and sickle cell trait, and malaria.

The reason for this diffusion must be sought in the multiple metabolic functions that iron performs.
Just to mention the most important ones. Table 1

BIOLOGICAL FUNCTIONS OF IRON			
HEMOPROTEINS	**FUNCTION**	**NON-HEME IRON PROTEINS**	**FUNCTION**
Hemoglobin	O2 transport	Fe-S proteins	Respiratory chain
Myoglobin	O2 reserve	Aconitase	Krebs cycle
Cytochrome oxidase	O2 utilization	Succinate dehydrogenase	Krebs cycle
Cytochromes	Electron transport	Phosphoenol pyruvate carboxylase	Gluconeogenesis
Cytochrome P450	Detoxification	Dioxygenase	Collagen synthesis
Peroxidase	H2O2 utilization	Ribonucleotide reductase	DNA synthesis
Catalase	H2O2 utilization	Lactoferrin	Antimicrobial
		Ferritin	Reserve

Table 1: Biological Functions of Iron

Such an important metabolic commitment requires a constant and efficient supply of this element to maintain correct homeostasis.

According to the LARN its daily intake must be: 19.4 mg/day Table 2.

		Iron (mg/day)							
		Males				Females			
		Mean		P95[a]		Mean		P95[a]	
Population group, age range	N of surveys	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Infants, ≥4 to <12 months	3	2.6	6.0	5.7	9.4	2.8	5.5	5.7	9.0
Toddlers, ≥1 to <3 years	3	5.4	7.0	7.9	11.4	5.0	6.6	7.6	10.6
Other children, ≥3 to <10 years	6	8.3	11.5	12.3	17.3	7.5	10.6	11.0	16.3
Adolescents, ≥10 to <18 years	5	11.2	13.6	17.6	22.2	9.6	11.6	14.6	17.3
Adults, ≥18 to <65 years	6	12.6	14.7	19.4	23.1	10.2	11.6	15.8	18.6
Elderly, ≥65 to <75 years	6	11.9	15.0	18.3	24.5	9.4	11.1	14.7	17.6
Very elderly, ≥75 years	4	11.4	12.6	18.6[c]	18.6[c]	9.6	10.5	14.1[c]	14.1[c]
Pregnant women	1					14.7	17.9	34.9[c]	34.9[c]

Table 2: Scientific Opinion on the Tolerable Upper Intake Level for Iron, EFSA Journal. 2024;22: e8819 Legend
a. The 95th percentile estimates obtained from dietary surveys and population groups with fewer than 60 subjects may not be statistically robust (EFSA, 2011) and consequently are not considered in this table.
b. Minimum and maximum mean and 95th percentile estimates across European surveys, for each population group.
c. Calculated from one survey only.

It is clear that a healthy and correct diet does not always cover the daily requirement of this element, and it is equally clear why in underdeveloped countries and in the peripheries of the world iron deficiency, together with vitamin deficiency and anemia, are so widespread.These conditions are due to equally widespread malnutrition.The World Health Organization proposes for underdeveloped countries the use of functional foods enriched with nutrients lacking in the diet, to make up for their insufficient intake.Even in industrialized countries, paradoxically, excessive food consumption does not guarantee the essential nutrients for well-being.This is because the food we consume is poor in nutritional value and full of preservatives and additives.

However, in these countries the lack of essential nutrients is compensated for by the use of food supplements, which, as the name suggests, integrate the diet with those substances that industrially produced food contains in small quantities or does not contain at all.As regards the iron present in supplements, it is necessary to clarify the various types of iron present on the market.

The competitors on the market that offer supplements containing iron are divided into two types:
Supplements that contain iron pyrophosphate, which are the vast majority, and those that contain iron sulphate.

Different Types of Iron

Let's distinguish the differences between the two iron salts from the chemical point of view and their biological value.First of all, we must emphasize that the chemical properties and the structural difference between the two salts have important consequences for their absorption and assimilation.

In fact, the iron pyrophosphate salt has a very high molecular weight of 745.21 Daltons, while iron sulphate has a lower molecular weight, equal to 151.90 Daltons.This means that to ensure the same daily iron intake of approximately 20 mg/day, in compliance with the LARN, with ferrous pyrophosphate one must administer a quantity of substance approximately three times greater than with ferrous sulphate: 745 g, versus 152 g, Figure 5.

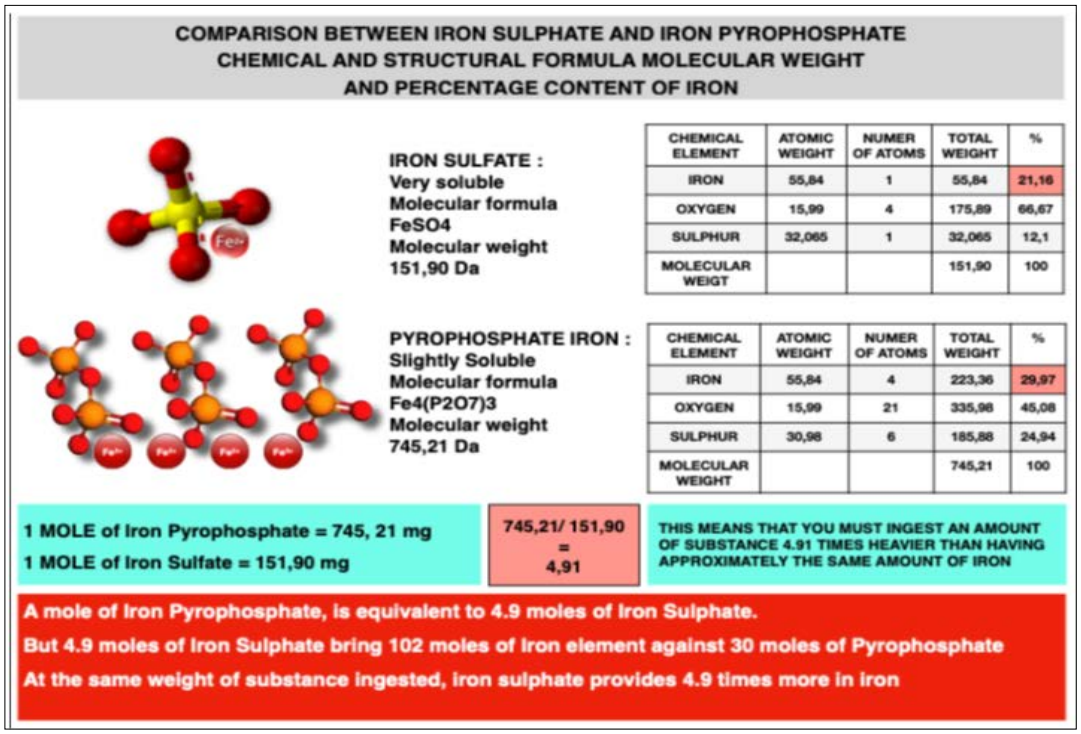
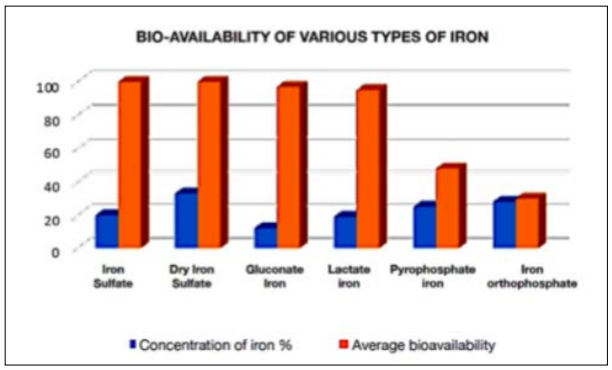


Figure 5: Comparison between Iron Sulphate and Iron Pyrophosphate

Furthermore, the bioavailability of the two salts is very different and that of iron sulphate is much greater than that of iron pyrophosphate [3-6].

It is known that at pH levels above 3 the Fe 3+ ion tends to form Fe (OH) 3 which has practically zero solubility in water. In fact, the bioavailability of Fe 3+ is very low due to its low solubility at the physiological pH of the intestine. For this reason, the organism has developed an efficient transport system [5].

This means that a greater amount of iron pyrophosphate must be administered to obtain a biologically equivalent dose of iron from the two salts, with an additional metabolic load, Figure 6.



Iron Compound	Approximate Fe (%)	Average Relative Bioavailability: Rat	Average Relative Bioavailability: Man	Potential for Adverse Organoleptic Changes: Color	Potential for Adverse Organoleptic Changes: Fat Oxidation	Approximate Relative Cost*
Freely water soluble						
Ferrous sulfate $7H_2O$	20	100	100			1.0
Dried ferrous sulfate	33	100	100			0.7
Ferrous gluconate	12	97	89			5.1
Ferrous lactate	19	—	106	high	high	4.1
Ferric ammonium citrate	18	107	—			2.1
Ferrous ammonium sulfate	14	99	—			2.1
Ferric choline citrate	14	102	—			11.0
Poorly water soluble/soluble in dilute acid						
Ferrous fumarate	33	95	100			1.3
Ferrous succinate	35	119	92			4.1
Ferric saccharate	10	92	74			5.2
Ferric glycerophosphate	15	93	—	low	low	10.5
Ferrous citrate	24	76	74			3.9
Ferrous tartrate	22	77	62			3.9
Water insoluble/poorly soluble in dilute acid						
Ferric pyrophosphate	25	45–58	21–74			2.3
Ferric orthophosphate	28	6–46	25–32			4.1
Elemental Fe powders:						
electrolytic	97	16–70	75			—†
H-reduced	97	13–54	13–148	negligible	negligible	—†
Co-reduced	97	12–32	ND			—†
atomized	97	ND	ND			—†
carbonyl	99	35–66	5–20			—†

* Relative to ferrous sulfate $7H_2O$ = 1.0, for the same level of total iron.
† In general less expensive than ferrous sulfate. Cost of different powder types varies approximately sevenfold, with carbonyl iron being the most expensive.
ND = not determined.
Source: adapted from Hurrell, reference 2.

Figure 6: Comparison of Bioavailability between Various Types of Iron

Most micronutrients present in supplements have poor solubility and bioavailability, which leads to reduced nutritional intake and insufficient coverage of LARN.To overcome these drawbacks, various technologies are used, which facilitate the transport and absorption of substances.Only in some cases are advanced technologies adopted with the use of special pharmaceutical forms that improve the bioavailability and organoleptic properties of nutrients.The most frequently used technologies are Micronization, Microencapsulation Figure 7 and, very rarely, Liposomal Technology , Figure 8 and finally Sucrosomial technology [6-9]. But even in this respect there are clear differences.

Technology Comparison

Micronization and Microencapsulation

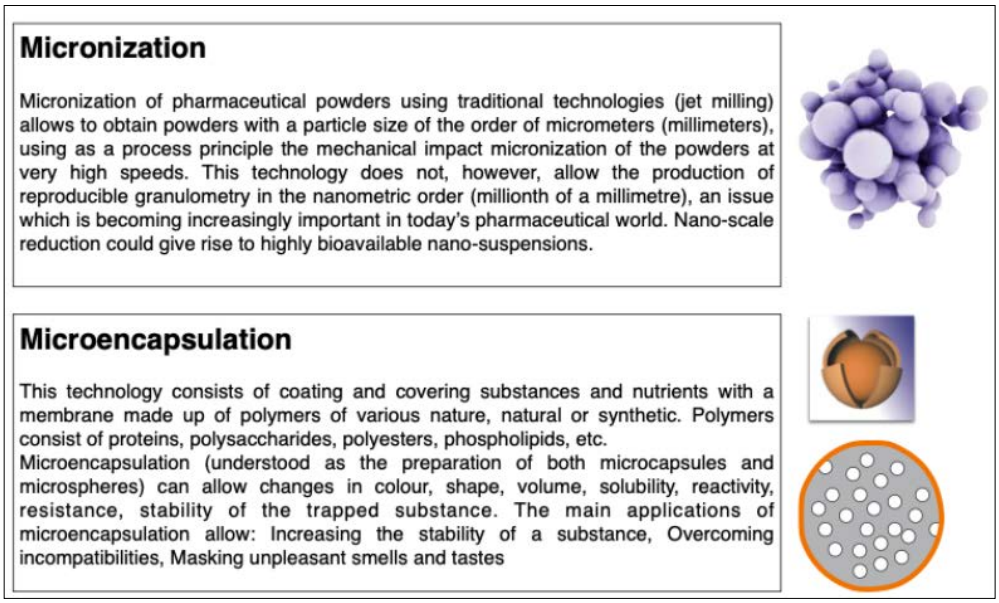


Figure 7: Schematic Representation of Micronization and Microencapsulation

Liposomal Technology

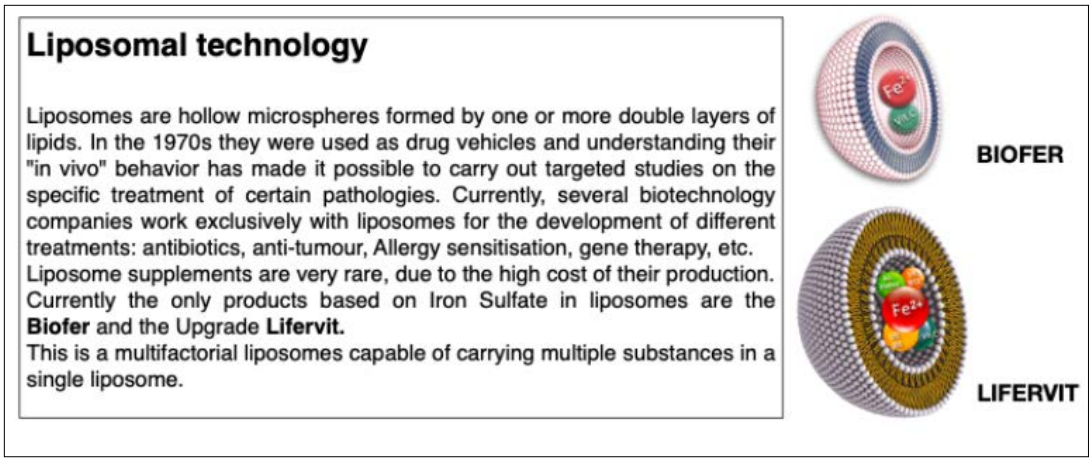


Figure 8: Schematic Representation of Liposomes

Sucrosomial Technology

For some years now, a new system for the administration of Iron has been marketed, called " Sucrosome ", formed on the basis of a fatty acid with sucrose. Since this technology has had considerable commercial success, we will carefully examine its characteristics.

We report the definition that the manufacturing company provides on the product Figure 9.

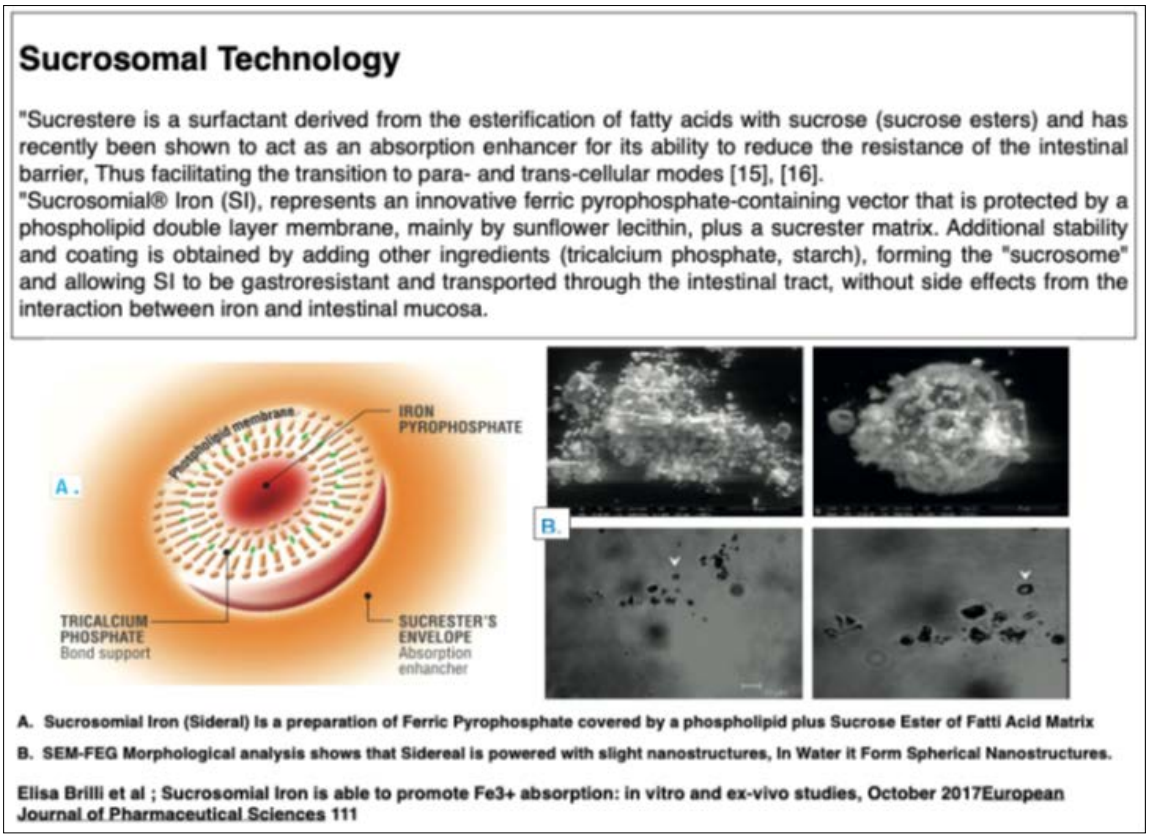


Figure 9: Schematic Structure of Sucrosomial Iron

Some Comments on the Technology

Sucrosomial Iron ® is an innovative oral iron technology, in which iron pyrophosphate (trivalent iron) is wrapped in a matrix of phospholipids and fatty acid sucrose esters. This structure is called Sucrosome ® which allows for high iron absorption and excellent gastrointestinal tolerability." As the same Agency describes the sucresters "acts as an absorption enhancer for its ability to reduce the resistance of the intestinal barrier, thus facilitating the transition to para- and trans-cellular modes".

1. First of all, we note that the iron used in this carrier is Iron Pyrophosphate, with all the limitations that this salt presents in terms of absorption and bioavailability, described above and schematized in Figure 3.
2. On Sucrosomial Iron, while there is only one questionable documentation on the morphological properties of the product [10-12].
3. Sucrose esters do not have such a good reputation, although they are widely used in the food industry as "emulsifiers" of butter, margarine, mayonnaise, ice cream, etc. Several works have highlighted the potential risks associated with their excessive use: [13-15].
4. While an alarming documentation is reported on the Iron Sucrose administered intravenously, present in the USA and other countries, as a drug with the trade name VENOFER [16-19].

Iron Metabolism

We describe iron metabolism in its fundamental aspects without going into the details of the complex biochemical and molecular mechanisms, which are beyond the scope of this article, but we will only indicate the fundamental steps of metabolism to identify the salient points and the enzymes involved.

Much progress has been made in describing the different key mechanisms responsible for iron metabolism. Among these, the role of Ferritin for iron storage, the Transferrin receptor (TfR), the iron regulatory protein (IRP) reversibly linked to iron-dependent response factors (IRE) and their respective messenger RNAs, mRNAs , have been elucidated .

The translation mechanism of iron carrier proteins and its transport depends on its concentration, such as the production of Divalent Metal Transporter I (DMTI), responsible for the absorption of ferrous iron from the brush border of duodenal enterocytes, and Ferroportin (Ireg1), responsible for the export of ferrous iron across the basolateral membrane of the same enterocytes. Ferric reductase converts ferric iron, Fe 3+ , into ferrous iron, Fe 2+ by means of DMTI, and Hephaestina , the membrane-bound ferroxidase , converts ferrous iron into ferric iron, creating an iron concentration gradient across the cell membrane that facilitates iron release. In conditions of low iron concentration, the translation of TfR , DMT1 and Ferroportin is increased, while at high iron concentration it is reduced.

We have schematically represented the iron metabolism with a summary table of the key steps, Table 3.

IRON METABOLISM
Dietary iron derived from both plants and animals and is mostly **in the ferric (Fe3+), is mainly composed of poorly absorbed inorganic iron, which is found in food.**
Heme iron, primarily present in animal food sources like meat, though less abundant is more bioavailable. **The first step of duodenal iron absorption is the transport of ferrous (Fe^{2+}) iron by DMT1** at the apical surface of enterocytes.
Previous reduction of the predominant Fe3+ by Dcytb is necessary. Iron bound to heme is internalized by a still unknown importer and iron is then released in the cytoplasm by the degradative action of heme oxygenase (HO-1). Following the brush border transit, both the iron imported by DMT1 and that liberated from heme enter the **labile iron pool (LIP)** and are either utilized, incorporated in ferritin shells or exported by ferroportin. PCBP1 and PCBP2 function as chaperones that deliver iron to client proteins.
At the basolateral surface, following the efflux of Fe^{2+} into the bloodstream by **Ferroportin**, the oxidative action of **Hephaestin** and **Ceruloplasmin** is required for the binding of Fe^{3+} to circulating transferrin.

Table 3: Summary of Iron Metabolism

And schematization of the salient passages, Figure 10

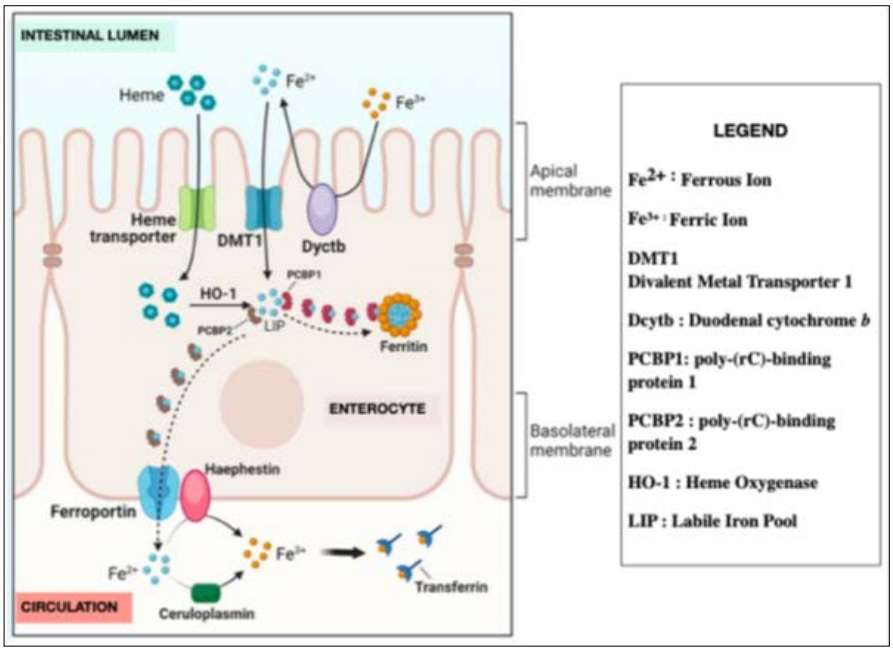


Figure 10: Diagram of Iron Metabolism

Iron Deficiency and Anemia
From a clinical point of view, iron deficiency must be distinguished from various forms of anemia that have different causes.

Iron Deficiency
It is the most widespread micronutrient deficiency in the world, affecting 1.2 billion people, 20% of the world's population.
It is divided according to the causes:

Physiological Causes
Some physiological stages involve increased iron losses or increased needs:

Menstrual Bleeding, Pregnancy and Breastfeeding, Vegetarians, Elderly

Pathological Causes

- Inadequate absorption: - intake of foods poor in iron - high stomach pH
- Intestinal mucosal dysfunctions
- Inflammatory processes at intestinal level
- Hormonal disorders
- Iron transport defects
- Traumas

There are 3 different levels of iron deficiency:
Level I: reduction of the Faith medullary reduction Ferritin silky (<20 mic /l) increase transferrin
Level II: everyone the previous And appearance of reduction sideremia, with increase PLE (Free Erythrocyte Protoporphyrin)
Level III: all the previous and appearance of: reduction Hemoglobin (++) And reduction erythrocytes (+) =

Definition of Anemia
Reduction in the total amount of hemoglobin circulating in peripheral blood, erythrocytes. By convention, reference is made to the concentration of Hemoglobin HB:

MEN WOMEN
Hb < 13 g/dl Hb < 12 g/dl

Classification of Anemias

- For reduced production of red blood cells (bone marrow aplasia, neoplastic infiltration of the bone marrow, B12 and folate deficiency, myelodysplasia)
- For Hemoglobin Synthesis Hb , abnormal or reduced, iron deficiency, from chronic disorders (inflammations, infections, neoplasms) Thalassemia, abnormal Hb , chronic renal failure, endocrinopathies ;
- For Increased red blood cell destruction;

Intracorpuscular Causes: membrane alteration, anaerobic glycolysis, hexose phosphate shunt deficiency, qualitative alterations of Hb
Extracorpuscular Causes: mechanical causes, isoimmune or autoimmune hemolytic diseases.

Iron Deficiency and Megaloblastic Anemias
Iron deficiency anemias are due to iron deficiency, megaloblastic anemias are due to vitamin B12 or folic acid deficiency, Figure 11.

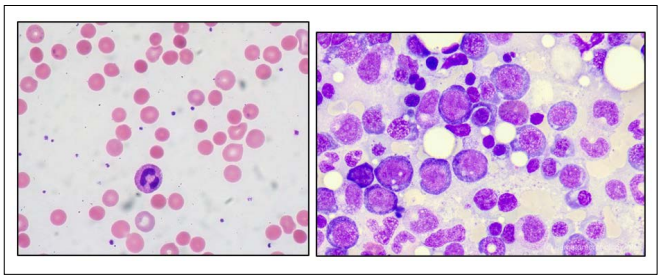


Figure 11: Sideropenic Anemia and Megaloblastic Anemia

Iron-Based Supplements
Let's see what the morphological and efficacy aspects are among traditional iron-based supplements
and Iron sulphate in Liposomes, Table 4.

Characteristic	Liposomal iron	Conventional Iron
Phospholipid Bilayer	Present	Absent
Effect of gastric acidity	None	Present
Oxidation of iron	No	Yes
Targeted iron delivery	Yes	No
Absorption of iron	Enhanced	Regular
Absorption via intestinal M cells	Yes	No
Food effect	No	Yes
Oxidative damage to intestinal epithelium	No	Yes
Gastrointestinal side effects	Minimal/Absent	Yes
Metallic taste	No	Yes
Chelation with other metals	No	Yes

Table 4: Differences between Liposomal Iron and Conventional Iron

Microencapsulated Iron Pyrophosphate
For the iron pyrophosphate produced by Lipofood (Lipofer brand), which is the main supplier of raw materials for all the supplements on the market, there is no documentation of the morphology observed under the electronic microscope or measured with granulometry .

Iron sulphate in liposomes
There are only two products of iron sulphate in liposomes in the world: Biofer and the Lifervit Upgrade, both are patented and trademarked.

There are several works that have documented both their morphology and bioavailability Figure.12 [20-26].

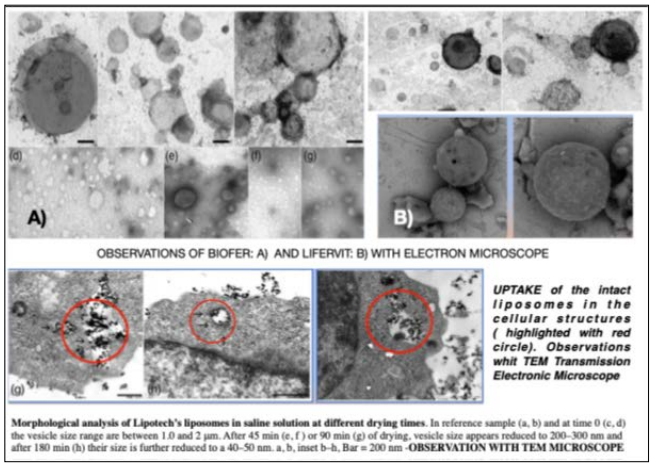


Figure 12: Uptake of the intact liposomes in the cellular structure (highlighted with red circle), Observations whit TEM Transmission Electronic Microscope

In a study with radiolabeled iron, Biofer also demonstrated a preferential tropism for haematopoietic organs. [27] Figure 13.

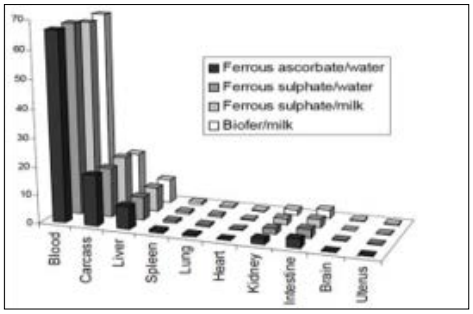


Figure 13: Iron Distribution in Different Organs

Biofer was the first product in the world based on Iron sulphate in Liposomes, patented in 1975, followed by Lifervit based on Iron sulphate, Vitamin C, Folic Acid, Vitamin B6 and Vitamin B12, contained within each single liposome, Multifactorial Liposome, Figure 6.

The rationale for the formulation of Lifervit with three substances is based on the understanding that iron administered individually is necessary but not sufficient to ensure correct erythropoiesis, but it is essential to combine iron with at least folic acid, plus Vitamin B6 and Vitamin B12, to also treat megaloblastic anemia [28-30].

Furthermore, the association between Folic Acid, Vitamin B6 and Vitamin B12 is necessary to prevent Hyperhomocysteinemia , an independent cardiovascular risk factor [31-33].

The Lifervit technology has been patented and the Trademark has been registered, but no case studies have been presented yet. While for Biofer there is a large literature that documents the actual liposomal morphology and efficacy.

In this article we present and discuss a first significant case study on LIfervit.

Lifervit Case Study in Oncology Patients
Lifervit is used in these patients to improve iron levels and support the immune system. Additionally, supplementation with Lifervit may have beneficial effects on blood counts, but the specific benefits depend on the individual patient's condition and the type of cancer treatment they are undergoing.

Benefits of Blood Count in Cancer Patients

Increased Iron Levels
Iron supplementation can be especially helpful for cancer patients who suffer from anemia, a common condition caused by both the disease and treatments such as chemotherapy. Iron is essential for the production of hemoglobin, the protein that carries oxygen. By taking iron and vitamins through Lifervit, you help support the production of red blood cells, which can improve blood counts and reduce symptoms associated with anemia (such as fatigue and weakness).

Immune System Support
Vitamins such as vitamin C and B vitamins in Lifervit are important for the functioning of the immune system. In cancer patients, the immune system is often compromised by both the disease and the treatments (such as chemotherapy and radiation). Supplementing with these vitamins helps to strengthen the immune response.

Improved Red Blood Cell Synthesis
Folic acid, present in Lifervit, is involved in DNA synthesis and the formation of red blood cells. Supplementation with folic acid and Vitamin B12 is useful in patients with megaloblastic anemia, a condition that can occur during and after cancer treatment.

Reduction of Fatigue
Since anemia can cause fatigue and reduce the quality of life in cancer patients, supplementing with Lifervit helps improve energy levels and reduce tiredness, promoting a better recovery of general well-being.

Before starting supplementation, it is essential that cancer patients consult with their doctor to evaluate the possibility of such supplementation. Sometimes, anemia in cancer patients may be due to other causes, such as blood loss or disease-related problems, and not just iron or vitamin deficiencies.

Individualized Dosage
The dosage of iron and vitamins must be adjusted to the specific needs of the patient, based on the type of cancer, treatments received, and the levels of iron and vitamins in the blood. Excessive iron intake can cause unwanted side effects, such as liver damage.

Materials and Methods

Postmarketing Study Surveillance
This study collects the "observational" results detected on a group of 50 oncological patients treated with basic oncological therapy and adjuvant therapy with the Lifervit supplement for three months, 12 weeks.The study design is Post Marketing Surveillance and follows the guidelines of the Ministry of Health and other important institutions [34-35].

Surveillance (PMS) studies include procedures for monitoring patients undergoing treatment with drugs or supplements used in clinical practice. Unlike the procedures of clinical trials performed in the premarketing phase in which it is essential to respect rigorously controlled methodological conditions, in Post Marketing Surveillance fidelity in data collection is required to monitor the safety of use of the tested products over time. However, PMS studies can provide valuable information on the use of the products sold, in special patients or with particular problems, which are not easily obtainable or predictable during premarketing studies.

Design
The aim of this work is to evaluate the safety of use and tolerability of Lifervit, a supplement based on iron sulphate and B vitamins in liposomes, in oncological subjects undergoing specific therapy.

This is a simple open-label study with monitoring of haematological parameters, daily life, and fatigue (Data on confidential file)

Criteria
Oncology patients aged between 35 and 77 years; of both sexes who were asked to provide written informed consent

Enrolled patients with varying degrees of anemia were monitored at the beginning and end of treatment by recording the following parameters:

Hematocrit, Hemoglobin, Iron (sideremia), Ferritin, Transferrin
The values of the parameters under consideration for inclusion were:

hemoglobin ≤ 12 g/ dL ; ferritin ≤ 100 ng/ mL or Ferritin between 100 and 200 ng/ mL with transferrin saturation (TSAT) ≤ 25%, Sideremia < 40 µg/ dL.

Patients who developed anemia with previous unsuccessful treatments were also included.

Questionnaire and Registration

Administration of a Questionnaire for Anamnestic Investigation

The first part of the questionnaire concerns the personal and social characteristics and eating habits, personal medical history, relative to familiarity with oncological diseases. (Confidential data).

Other Data Collected

Age, Ethnicity, Smoking, Physical activity, BMI, Diet.

Exclusion Criteria

Patients with the following were excluded:
blood transfusions, intravenous or oral iron therapy in the last three months;

Duration of Treatment

Patients were treated for a minimum of three months or until normal values returned, if they did not present intolerance problems, in which case treatment was interrupted.

Discontinuation of Treatment

Patients not responding to treatment after two months were excluded from the study;
Patients who experienced significant side effects during treatment, which were definitely attributable to the treatment itself and not to other concomitant therapies, were excluded and the side effects reported.
During the study period, no changes were made to the ongoing basic oncological therapy, and the patients' diet was not modified.

Case History

The treated patients were recruited in various Italian regions.
In 11.8% of the treated cases, the patients were coming from treatments with drugs or iron-based supplements to which they were non- responders.

For the treatment of patients, we used the product notified to the Ministry of Health: LIFERVIT described above.

Patients were treated with 1 capsule per day of the mentioned product.
All patients were asked to give informed consent, and they also had access to the adverse event reporting form and any intolerances encountered during treatment.

In order to evaluate the efficacy of Lifervit in the management of oncological patients, we treated 50 patients with stage 4 disease, recording the starting hematocrit values and the motor and energy functional parameters, using the Karnofsky scale.

Karnofsky Index (Karnofsky Performance Status, KPS)

It is one of the most widely used tools in oncology medicine to assess the functional status and energy of a patient. It is used to determine the patient's ability to perform normal daily activities and to monitor the effectiveness of a treatment, as well as to predict the prognosis.
Karnofsky Index is a numerical scale ranging from 0 to 100, where:
- 100 indicates that the patient is completely asymptomatic and able to carry out all normal daily activities.
- 0 represents the patient's death.
- Intermediate scores indicate various levels of disability, from complete physical well-being (100) to severe disability (0).

The index is particularly useful for measuring:
- The effect of chronic diseases, such as cancer, on the patient's physical and energetic state.
- The impact of cancer treatments (such as chemotherapy or radiation therapy) on the patient's ability to function.
- The assessment of the patient's self-sufficiency, that is, his ability to take care of himself,
in daily activities, and in social interaction.
Karnofsky Index is structured on a scale that provides a numerical evaluation of the patient's performance. The scale scores are as follows Table 5

Table 5: Karnofsky Performance Scale

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disable; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

In our observational study, we assigned all study patients an initial Karnofsky score between 50 and 60.

These were patients with pancreatic, breast, lung, hepatobiliary and prostate cancer.All treated subjects were adults, ranging in age from 35 to 77 years.We took into consideration, as a fundamental clinical reference, the blood count values at the time of enrollment and compared them with the subsequent ones during chemotherapy treatment.After the combined therapy with allopathic and complementary drugs we were able to assign a KARNOFSWKY SCALE value between 70 and 90 to all patients who received Lifervit supplementation.As is well known, following single-drug or combination antitumor treatments, the blood chemistry parameters of all patients tend to worsen. And this is what we observed in all patients to whom, as already underlined, we had assigned a Karnofsky index between 50 and 60 points.We detected an anemic syndrome with hypoglobulia and sideropenia in all 50 treated patients. The recorded values are reported in Table 6.

Lifervit therapy was started immediately while monitoring tumor growth parameters.

Hematochemical parameters of neoplastic growth are measurable indicators in the blood that can determine the presence, progression or activity of a tumor.

We collected the values of the most important oncological markers, but they were not compared during the treatment.

- **Specific Tumor Markers**
  CEA (Carcinoembryonic Antigen) → Associated with colorectal, lung, breast, and pancreatic cancers.
  CA 19-9 → Indicator of pancreatic and gastrointestinal tumors.
  CA 125 → Used to monitor ovarian cancer.
  CA 15-3 and CA 27-29 → Associated with breast cancer.
  AFP (Alpha- fetoprotein) → Elevated in liver and testicular tumors.
  PSA (Prostate Specific Antigen) → Used for prostate cancer.

- **Proliferation and Inflammation Indicators**
  LDH (Lactate Dehydrogenase) → Increased in many tumors, related to rapid proliferation.
  Beta-2 Microglobulin → Indicator of hematological malignancies such as multiple myeloma and lymphomas.
  CRP (C-Reactive Protein) → Often elevated in advanced tumors with an inflammatory component.
  ESR (Erythrocyte Sedimentation Rate) → Nonspecific value, but may increase in case of tumors.
- **Neoangiogenesis Factors and Tumor Microenvironment**
  VEGF (Vascular Endothelial Growth Factor) → Involved in the formation of new blood vessels in tumors.
  TGF-β (Transforming Growth Factor Beta) → Regulates tumor growth and the immune system.
- **Metabolic Alterations**
  Glucose and Insulin → Some tumors can alter glucose metabolism.
  Ferritin → May be elevated in tumors with inflammatory response.

- **Immune System Parameters**
  Lymphocyte count and neutrophil-to-lymphocyte ratio (NLR) → Indicative of inflammatory response and prognosis in some tumors.
  Interleukins (IL-6, IL-8, IL-10) → Associated with tumor growth and immunosuppression.
  These parameters taken individually have no absolute diagnostic value, but can be used to monitor disease progression, response to therapy and prognosis.

Results

After the 12-week treatment period, we collected the results obtained in the Table. 6, which reports differences in the parameters evaluated before and after treatment Table 6.

We have already mentioned the relative reliability of the results obtained, both for the reduced case history and for the heterogeneity of the pathologies considered. For this reason, we did not carry out a statistical evaluation of the results obtained. We just wanted to have a first result to see if the adjuvant therapy could bring some benefit in relieving patients' fatigue.

In any case, patients were informed of the study's objective, and we asked for informed consent before treatment.

Table 6: Summary Results Obtained after Treatment of 50 Patients

Patient with Cancer, Initial and Final Values, after treatment with Lifervit (12 weeks of therapy)				
Hematoclinical Parameters	**Normal Average Values**	**Inizial Average Values (*)**	**Final Average Values**	**Observations**
Hemoglobin (g/dl)	13-17 g/dL	7-10 g/dL	10-13 g/dL	Improved but not completely recovering
Red blood cells (RBC)	4.7-6.1 milioni/µL	3,0 - 4,2 millions /µL	3.8-4.8 millions/µL	Increasing
Hematocrit (Hct) %	42-52%	25 - 35 %	30-38%	Increasing
Mean Corpuscolar Volume (MCV)	80-100 fL	< 80 fL	78-90 fL	Gradually increasing
Average Hemoglobin Content (MCH)	27-33 pg	< 27 pg	26-30 pg	towards normalisation
Serum Iron. (µg/dL)	50-170 µg/dL	<40µg/dL	50-100 µg/dL	Recovery of Iron levels
Ferritin (ng/ml)	20-250 ng/mL	<15-30 ng/mL	50-150 ng/mL	Levels increased
Transferrina Saturation	20-50%	< 15%	20-35%	Increasing

OBSERVATION: (*) These values indicate a typical iron deficiency sideropenic anemia, common in cancer patients with blood loss or reduced intestinal absorption.

After the combined therapy with allopathic and complementary drugs, we were able to assign a value of Karnofsky performance ranging between 70 and 90 to all patients who received Lifervit supplementation.

Conclusion

The aim of this article was to evaluate the observational results of safety and efficacy of Lifervit on a first case series limited in the number of patients involved, but very challenging with regard to the fragility of the patient's undergoing treatment.

For this reason, we paid particular attention to the possible side effects that the adjuvant therapy adopted could generate.

We also stress that, although the small number of cases and the heterogeneity of patients treated did not allow us to statistically evaluate the results, we are very satisfied with the positive effects obtained with the supplement used.

The use of Lifervit has produced positive effects in treated patients, improving both blood chemistry parameters and energy levels. This supplement can support the management of anemia, improve immune function and promote greater energy during cancer treatments. However, it is always of fundamental importance to work closely and in tune with the medical team to ensure that the supplementation is safe, effective and personalized. The improvements observed in our patients represent a success in terms of symptomatic therapy but require continuous monitoring to optimize long-term results and avoid that vitamins and iron may have anabolic effect for.

Disclosure

The authors state that there are no conflicts of interest in this study

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