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Relatório de Estágio e Monografia intitulada "Parkinson's disease: Innovative pathways underlying the etiology and the therapeutics via modulation of the gut microbiota" referentes à Unidade Curricular "Estágio", sob a orientação, respetivamente, do Dr. Orlando António Fernandes Gonçalves e do Professor Doutor João António Nave Laranjinha apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

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Ricardo Manuel Esteves Ribeiro

Parkinson's disease:

Innovative pathways underlying the etiology and the therapeutics via modulation of the gut microbiota

Orientador: Professor Doutor João António Nave Laranjinha

Relatório de Estágio em Farmácia Comunitária

Orientado pelo Dr. Orlando António Gonçalves Fernandes, na Farmácia Gonçalves.

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Coimbra, 5 de setembro 2018.

Ricardo Manuel Esteves Ribeiro

(Ricardo Manuel Esteves Ribeiro)

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A todos vocês o meu mais sincero OBRIGADO.

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Acronyms

DA - Dopamine

DAn - Dopaminergic Neurons

DMV - Dorsal motor nucleus of the vagus

ENS - Enteric Nervous System

GI - Gastrointestinal

NMS - Non-motor symptoms

PD - Parkinson's Disease

PUFAs - Polyunsaturated fatty acids

SCFAs - Short-Chain Fat Acids

SNpc - Substantia nigra pars compacta

Abstract

Recent studies show an intimate and complex bi-directional communication pathway between the brain and the gut involving the microbiota: the microbiota-gut-brain axis. This communication network may be the determining factor in the progression of certain neurodegenerative diseases, namely Parkinson's disease. It has been shown by several studies that changes in the intestinal microbiota triggers a series of cellular mechanisms that lead to an exaggerated inflammatory process that weakens the integrity of the intestinal epithelium. This imbalance in the permeability of the intestinal epithelium exacerbates the inflammatory response which spreads to the enteric nervous system, contributing to the formation of α-synuclein aggregates. Due to the connection between the enteric nervous system and the central nervous system through the vagus nerve, inflammation and α-synuclein aggregates spread to the central nervous system, where occurs deposition of α-synuclein in the neurons of the substantia nigra. However, alternative therapies based on phospholipidic membrane precursors, probiotics, prebiotics and synbiotics relied on a neuroprotective and anti-inflammatory effect and could therefore represent a new approach to the treatment of Parkinson's disease. Here we critically address these novel and innovative pathways underlying both PD etiology and therapeutic intervention.

Resumo

Estudos recentes, evidenciam uma íntima e complexa via de comunicação bidirecional entre o cérebro e o trato gastrointestinal envolvendo o microbiota: o eixo cérebro-intestino-microbiota. Esta rede de comunicação entre o cérebro e o intestino pode ser o fator determinante na progressão de doenças neurodegenerativas, nomeadamente a doença de Parkinson. Tem sido demonstrado em vários trabalhos que alterações no microbiota intestinal desencadeia uma série de mecanismos celulares que levam a um processo inflamatório exagerado que, por sua vez, debilita a integridade do epitélio intestinal. Este desequilíbrio na permeabilidade do epitélio intestinal exacerba a resposta inflamatória a qual se propaga para o sistema nervoso entérico, contribuindo para a formação de agregados de α-sinucleína. Dada a ligação entre o sistema nervoso entérico e o sistema nervoso central, através do nervo vago, a inflamação e os agregados de α-sinucleína propagam-se até ao sistema nervoso central, onde ocorre deposição de agregados de α-sinucleína nos neurónios da substantia nigra. Contudo terapias alternativas à base de precursores de compostos fosfolipídicos, probióticos, pré-bióticos e simbióticos relavam um efeito neuroprotetor e anti-inflamatório, podendo assim representar uma nova abordagem a terapêutica da doença de Parkinson. Neste trabalho discute-se criticamente estas novas vias subjacentes à etiologia e à intervenção terapêutica na doença de Parkinson.

Introduction

Neurodegenerative diseases have been one of the growing challenges of modern medicine, not only because of the complexity adjacent to these pathologies, but also because the number of cases has increased considerably in the last decades due to the increase in the average life expectancy of the worldwide (Tysnes and Storstein, 2017).

Parkinson's disease represents the second most common neurological diseases today, affecting approximately seven million people globally, mainly individuals over sixty and for whom there is no therapeutic intervention until the moment that prevents its progression (Samii, Nutt and Ransom, 2004; Tysnes and Storstein, 2017). However, in the light of the most recent research, the microbiota-intestine-brain stands out as a possible new approach for new therapeutic targets, as well as pave the way for a better understanding of its pathophysiology (Perez-Pardo *et al.*, 2018).

1- Parkinson's Disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder worldwide (Poewe *et al.*, 2017)In fact, the prevalence of PD is 1 in 100 people over the age of 50 years (Balestrino and Martinez-Martin, 2017) and the diagnosis is usually made in the sixth or seventh decade of life. Although, there are rare cases where the disease can be found in people in their forties (Zou *et al.*,2013), being classified as a young onset – juvenile PD. Either way, PD is more prevalent in men than in women (Van Den Eeden *et al.*, 2003), as it has been suggested that a protective effect of female sex hormones, sex-associated genetic mechanism or sex-specific differences in exposure to external environmental risk factors might be the explanation for male prevalence (Poewe *et al.*, 2017). Based on the aging of population worldwide, specifically the in developed countries, the prevalence of the disease will drastically increase in the next several years(Jameson and Weetman, 2012).

PD is generally considered as a movement disorder, because is characterized by cardinal movement impairment, like bradykinesia (slowness in the execution of voluntary movements), instability (a tendency to fall even in the absence of weakness or cerebellar balance disturbance),muscular rigidity (stiffness), and tremor at rest, with an asymmetric onset, which becomes bilateral along time (Poewe *et al.*, 2017) These motor impairments are a direct effect of a progressive degeneration of dopaminergic neurons (DAn) in the nigrostriatal pathway at the level of the substantia nigra pars compact (SNpc) (Langston, 2006;), this result in a drastic reduction of dopamine release (DA) within the striatum multiple aspects of cognition, including both motor and action planning, reward perception, decision-making,

reinforcement, and motivation (Remy *et al.*, 2005)(Lees et al., 2009). Nevertheless, although it has been suggested that norepinephrine and serotonin are also low in PD patients, DA is the most drastically reduced (Shannak *et al.*, 1994), being this loss considered the main responsible for the appearance of the majority of PD motor signs.

However it has long been recognized that the symptoms go beyond motor dysfunction since the patients very often develop non-motor symptoms, including cognitive impairment (Aarsland *et al.*, 2017), hyposmia (Haehner, Hummel and Reichmann, 2009), depression (Remy *et al.*, 2005), orthostatic hypotension (Lim and Lang, 2010), tiredness and the most common, gastrointestinal (GI) dysfunction (Savica *et al.*, 2009; Pfeiffer, 2011; Fasano *et al.*, 2015) .

Although all PD focus is almost directed to its motor symptomatology, there are recent studies indicating that non-motor symptoms (NMS) are also a crucial feature of PD, strongly suggesting that they could precede, in many years, the appearance of the clinical PD motor symptoms (Owens-Walton *et al.,* 2018). This assumption is completely valuable, thereby indicating that, in addition of being a new potential approach for an early diagnosis of the disease, the elucidation of the physiopathology mechanism behind PD NMS could also be a potential target to improve and develop new PD treatment (Owens-Walton *et al.,* 2018). Despite all this the intensive studies carried out on the PD NMS, the current strategies in the treatment of PD are just being effective in the reduction and mitigation of its motor symptoms, but completely ineffective in NMS.

At this time, the understanding of how the pathology begins and how it progresses over time is still very poorly understood. Is of absolute importance that further studies shall be performed in order to correctly understand the (molecular and cellular) physiopathology mechanism that could be in the origin and development of PD motor and non-motor signs with the purpose of establishing a more precise and clear pathophysiology signature of PD and how approach new treatment therapies(Bastide *et al.*, 2015).

1.1- Pathology of Parkinson's disease

Clinically PD include neuronal loss in specific areas of the substantia nigra and widespread intracellular protein (α-synuclein) accumulation. Although neither the loss of pigmented dopaminergic neurons in the substantia nigra nor the deposition of α-synuclein in neurons is specific for Parkinson disease, these major neuropathologies are only specific for an objective and precise diagnosis of Parkinson disease when applied together (Poewe *et al.*, 2017).

In PD degeneration occurs only in certain types of neurons within particular brain regions. By the early-stage of the disease the loss of dopaminergic neurons is restricted to the ventrolateral substantia nigra not affecting other midbrain dopaminergic neuron, but with the development of the pathology becomes more widespread by end-stage disease (Dijkstra *et al.*, 2014). Several recent clinicopathological studies supports that the loss of these dopaminergic neurons even on early stages in the disease suggests that the degeneration in this region starts before the onset of motor symptoms (Iacono *et al.*, 2015) .

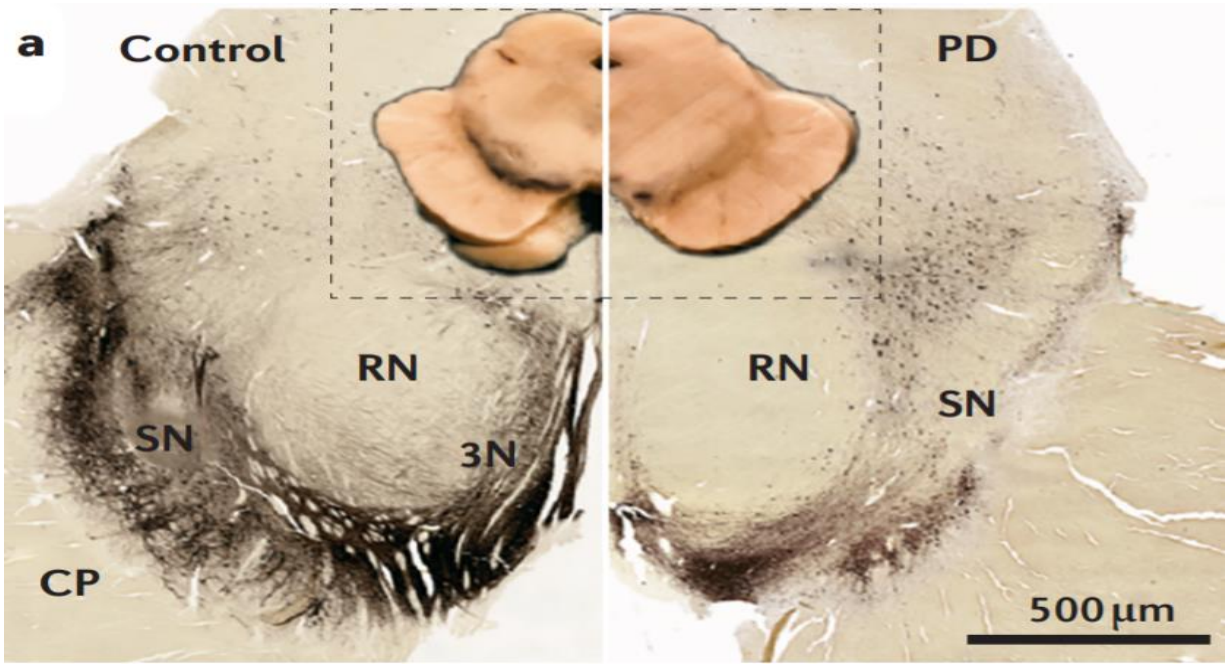

Figure 1- The depigmentation of susbstantia nigra (on the right) compared with the control with absence of pathology is one of the main hallmarks for Parkinson's disease. (Figure adapted from " Parkinson disease", Poewe W. *et al.* 2017)

The other neuropathology the define PD is the deposition and aggregation of α-synuclein in the cytoplasm of certain neurons in multiple different brain regions.

Synucleins are a family of relatively small, approximately 140 AA, soluble proteins discovered in 1985, found only in vertebrates and primarily expressed in neural tissue (mainly in presynaptic terminals) and in certain tumours. The alpha-synuclein (α-synuclein), beta-synuclein (β-synuclein) and gamma-synuclein (γ-synuclein) are the three different proteins belonging to this family that are knowing to this date. Although its function is not fully elucidated, it is thought to be related to the regulation of membrane stability according to some studies (George, 2002; Bendor, Logan and Edwards, 2013), however the same research states that the occurrence of mutations in α-synuclein may be the cause of early-onset PD,

which happens around the forties, and the abnormal accumulation of the protein is evident in almost every case of PD (George, 2002).

Lewys bodies, were the first α-synuclein aggregation to be described and studied over a century ago by Fritz Heinrich Lewy. Due to the development of more precise and advanced histopathological methods, a greater range of α-synuclein aggregates have been studied and described (Saito *et al.*, 2016). The Lewys bodies pathology primarily occurs in cholinergic and monoaminergic brainstem neurons and in neurons in the olfactory system but is also found in limbic and neocortical brain regions with disease progression. Braak and colleagues claim that Parkinson's disease is originated when a pathogenic agent enters the body via the nose or gastrointestinal system and travels into the central nervous system (CNS) (Ferman and Boeve, 2007). In fact Lewy bodies had been found in the enteric and peripheral nervous systems which supports their claim that in Lewy body pathology, the α-synuclein, selectively travels through the CNS, especially targeting thin and largely unmyelinated neurons (Braak *et al.*, 2003). In recent studies in vitro tissue culture have elucidated some of the following features, represented in Figure 2, that make α-synuclein an potential candidate as the main pathogenic factor directly implicated in the prion-like (prion is a misfolded protein that due to its abnormal 3-D conformation is conferred on it infectious properties associated with fatal neurodegenerative diseases) spread of PD pathology (Visanji *et al.*, 2014).

As represented in Figure 2, the transmission of α-synuclein from neuro-to neuron can happen by the release of α-synuclein via leakage from damage cells with compromised membrane integrity into the extracellular space (Figure 2-1). In case that the α-synuclein circulated in the extracellular space it could then directly translocate the cell membrane and penetrate to neighbouring neurons (Figure 2-2). Another possible mechanism is the transmission from a cell to another cell via conventional exocytosis and endocytosis (Figure 2-3) or they can be packaged into exosomes which are released and taken up by surrounding cells (Figure 2-4).

Two more mechanisms can explain the spread the α-synuclein between neurons, being one the formation of nanotubes making a direct connection between two neuron cells, eventually allowing α-synuclein to transfer freely from one neuron to another (Figure 2-5), and the other is the direct transmission of α-synuclein by direct synaptic contact between neurons (Figure 2-6) (Braak *et al.*, 2003; Visanji *et al.*, 2014; Rietdijk *et al.*, 2017).

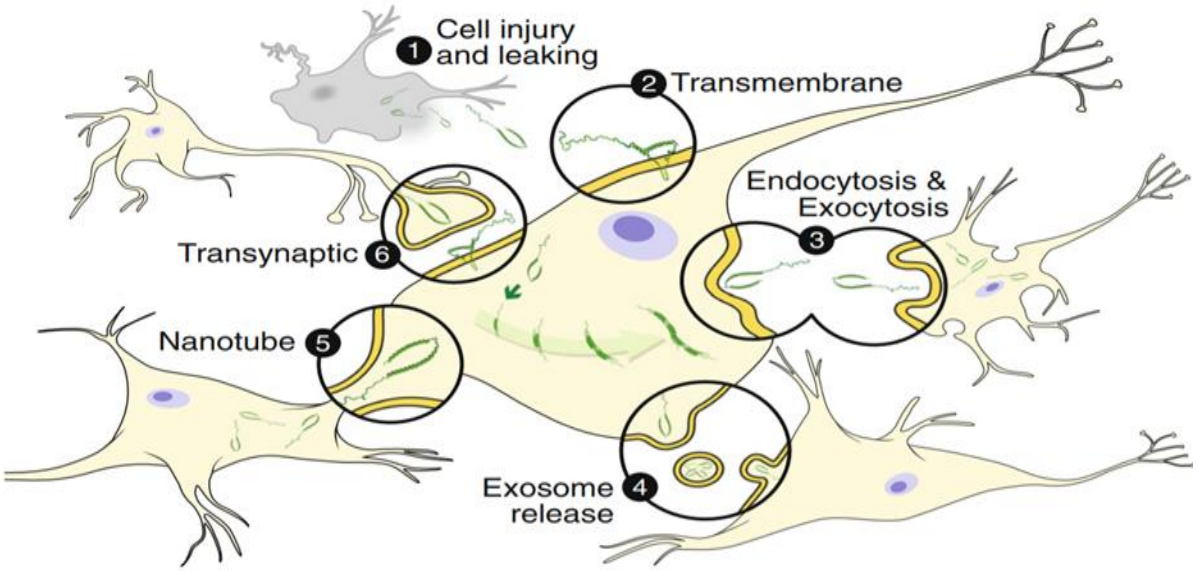

Figure 2- Representation of neuro-to-neuron mechanism of transmission of α-synuclein. (Figure adapted from ''The prion hypothesis in Parkinson's disease: Braak to the future', Visanji *et al*., 2014)

1.1.1-Braak's hypothesis for Parkinson´s disease

Braak and colleges postulated that the one possible cause of PD is a pathogen that enters the body via the nasal cavity, which is later swallowed and reaches the gut, initiating LP in the nose and the digestive tract. A staging system describing the spread of LP from the peripheral to the central nervous system was also postulated by the same research group although there has been some criticism to Braak's hypothesis, because not all cases of patients who developed PD follow this proposed staging system (Rietdijk *et al.*, 2017).

This hypothesis, illustrated in Figure 3, encompasses six different stages of progression, where in each stage is attributed an abnormal pathology in particular neurological structure. In terms of symptomatology, the type and severity of symptoms is correlated to progression through the Braak's stages. Early stages are characterized by non-motor symptoms, such as a lessened sense of smell or constipation. Motor symptoms commonly appear around the third and fourth stage, and cognitive symptoms arise as later Braak stages are reached (Braak *et al.*, 2003).

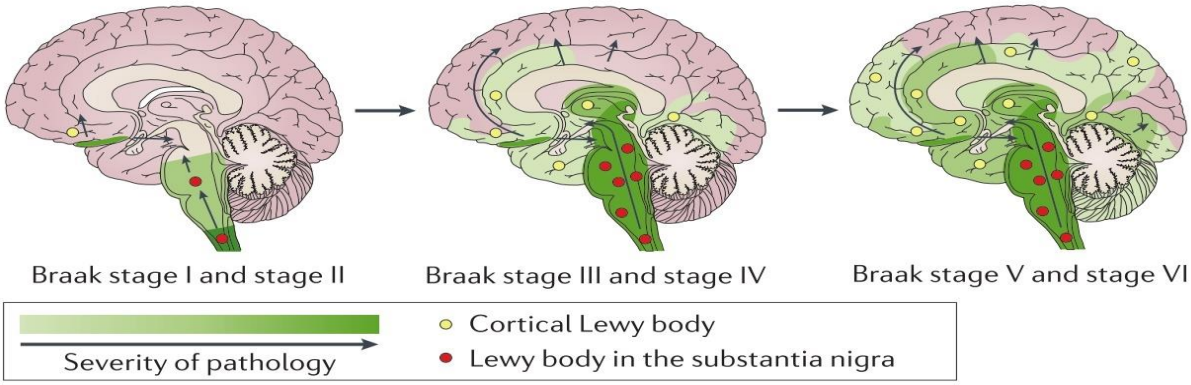

Figure 3- Hypothetical progression of α-synuclein aggregates, in the form of Lewis bodies. In stages I and II, the aggregates appear in the neurons of the lower brainstem, with most cases being asymptomatic. In stages III and IV, motor symptoms begin to appear due to infiltration of the aggregates in the intermediate brain and basal forebrain. In the final stages (stages V and VI), α-synuclein aggregates reach limbic and neocortical brain regions, completely invading the entire neocortex. (Figure adapted from ''Staging of Lewy pathology according to the Braak model'' Visanji *et al*., 2014)

1.1.2- Stages of α-synuclein progression

The formulation of a neuropathological staging allowed a better conceptualization of intriguing patterns of synuclein pathology in the brains of patients diagnosed with PD and a clear differentiation between the initial, intermediate and final stages of the lesions caused by this pathology. This is an important diagnostic tool because it allows a more specific view of the affected brain zones. However, the evaluation of the degree of involvement of the brain structures is considered less important than the evaluation of the anatomical distribution of the lesions, since it is only intended to construct an anatomical progression stage as shown in Figure 4 (Braak *et al.*, 2003; Rietdijk *et al.*, 2017).

Stage 1

The disease emerges from the enteric and peripheral nervous system and reaches structures of the lower brainstem and the olfactory system. Region like dorsal motor nucleus of the vagus nerve in the medulla oblongata are mainly affected by Lewy neurites, thread-like α-synuclein aggregates, which in this stage are more prevalent than globular Lewy bodies (Braak *et al.*, 2003).

Stage 2

In addition to the pathology observed in Stage 1, Stage 2 is characterized by additional lesions in more regions throughout the brainstem. The pathology then moves up the brainstem,

traveling from the medullary structures to the locus ceruleus reaching the pontine tegmentum. Similar to Stage 1, the presence of Lewy neurites outnumbers Lewy bodies(Braak *et al.*, 2003)

Stage 3

When reached Stage 3, the disease has entered the substantia nigra and lesions caused by Lewy bodies begin to form in the pars compacta. In the second half of this stage further structures are affected and the previous lesions from Stages 1 and 2 begin to develop more Lewy bodies (Braak *et al.*, 2003; Jellinger, 2009).

Stage 4

In Stage 4 is evident a severe dopaminergic cell destruction in the pars compacta. The involvement of allocortex and mesocortex begins while the integrity of neocortex remains unaffected (Poewe *et al.*, 2017).

Stage 5

The neocortex is invaded by the spread of α-synuclein and the pathology reaches structures of the frontal, temporal, and parietal lobes(Jellinger, 2009). Cellular death can be identified particularly in the substantia nigra but also the locus ceruleus and the dorsal motor nucleus of the vagus nerve, and (Braak *et al.*, 2003).

Stage 6

At this stage the pathology completely invaded all the neocortex, compromising the main motor and sensory areas in the brain. The disease is now at its most severe state and the motor and non-motor symptoms are exacerbated (Braak *et al.*, 2003; Jellinger, 2009; Poewe *et al.*, 2017).

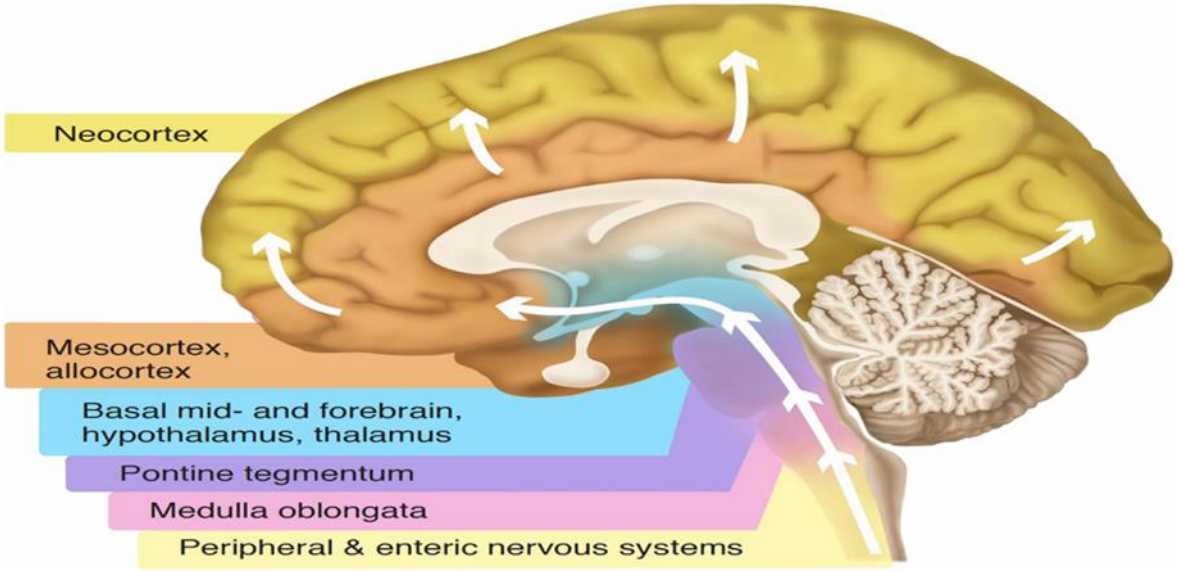

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Figure 4- Simple representation of the anatomical brain areas affected through the six Braak's stages of progression (Figure adapted from " Parkinson disease" from Poewe W. et al. 2017.)

1.2- Parkinson's Disease therapies

In the last decade, both basic and clinical research have attempted to establish new management strategies involving early diagnosis and a more in-depth assessment of the condition of patients with PD in order to develop and apply more effective strategies, thus establishing a personalized therapy, trying attenuate symptoms and improve the patient's quality of life (Diaz and Waters, 2009; De Sousa and Massano, 2013).

Although a there are promising approach in the treatment of patients with PD emerging over the last years, satisfactory approaches are still lacking of a significant impact, either for the relief or to delay the progression of PD, especially with respect to the protection of Dn from premature death (Onofrj, Bonanni and Thomas, 2008). Unfortunately, although promising results have been obtained experimentally and clinically with various drugs and surgical procedures, the lack of data demonstrating the delay of DAn loss / degeneration in PD remains the greatest challenge in its treatment (Diaz and Waters, 2009; Teixeira *et al.*, 2018).Despite the considerable scientific advances in recent years, the current treatment of PD depends only on the mitigation of its symptomatic impairments through the use of pharmacological strategies such as levodopa, which is still the gold standard in the treatment of PD, monoamine oxidase B, DA agonists and inhibitors of catechol-O-methyltransferase, all of which are only intended to compensate for AD deficits in the nigrostriatal dopaminergic

pathway(Dong *et al.*, 2016; Lindholm *et al.*, 2016; Magrinelli *et al.*, 2016). Although levodopa is widely used at the beginning of the disease because of its high level of control over parkinsonian motor symptomatology, the use of dopaminergic agonists, as pramipexole, are widely used because they can be used both at the onset of the disease and at more advanced stage (Cardoso and Camargos, 2006). When used as monotherapy in patients without previous treatment it is very useful in the control symptomatic of the disease and can also be used in combination with levodopa to avoid fluctuations (Lopes, Nishiyama and Tanaka, 2012).

Despite their proven effectiveness, studies have shown that they can cause undesirable side effects, conditioning and limiting their use for long periods of time (Onofrj, Bonanni and Thomas, 2008). In addition to all pharmacological treatments, surgical interventions such as deep brain stimulation, a neurosurgical treatment for neurological disorders using a cerebral pacemaker that sends electrical impulses to a specific part of the brain, has been used for reserved clinical situations where medication has not been effective and extensive damage to the patient. The procedures are used when antiparkinsonians have no effect on disease relief, been used as an alternative strategy for the treatment of PD (Kringelbach *et al.*, 2007; Okun, 2012).

However, even after surgical intervention, the progression of PD is neither avoided nor delayed and therefore does not represent a form of long-term treatment (Krack *et al.*, 2017).In addition to the use of molecular agents, the use of genetic engineering has also been developed and used as potential and promising strategies for the treatment of PD, presenting significant advances in the last decades (Amalric *et al.*, 2013; Seet *et al.*, 2014).

The increasing number of unsuccessful attempts to establish neuroprotective therapies in PD can be partially explained, according to several authors, by a simplistic approach of a single target, warning that more attention should be given not only to symptomatic differences but also to pathological differences between patients diagnosed with PD (Espay, Brundin and Lang, 2017). In fact, many other factors, such as oxidative stress, mitochondrial dysfunction, excitotoxicity, excessive inflammation, were also involved in the onset and progression of PD, in addition to DA degeneration and DA depletion. Thus, PD should be approached as a multifactorial neurodegenerative disease, possibly with several therapeutic targets to be explored (Kidd, 2000).

Therefore, it is necessary to find alternative therapies that do not target only the CNS as a therapeutic target, but rather targets that may be at the origin and progression of the

disease, thus contributing to a possible regression of the pathology or at least to prevent its progression (Perez-Pardo *et al.*, 2018).

2- Relation between Gastrointestinal Dysfunction and Parkinson disease

The presence of non-motor symptoms, years before the occurrence of motor symptoms in PD, were already noticed in the studies of James Parkinson, back in 1817. Despite nowadays the presence of this NMS are defined and correlated with PD, there isn't any kind of treatment for it (Chaudhuri *et al.*, 2010). This represents a negligent approach to the treatment, prevention and possible cure for PD, since NMS precede the most severe PD symptoms in many years and may be closely related to the origin of the pathology. It's therefore of utmost importance to recognize them as potential targets therapies and key points to establish new therapies (Chaudhuri and Schapira, 2009).

The Braak's model that theorizes the pathological progression of Lewy pathology in PD, which affirms that there is early involvement of the enteric nervous system (ENS) and the dorsal motor nucleus of the vagus (DMV), has caused special interest in the scientific community, in connection with the understanding and elucidation of the pathophysiological mechanisms adjacent to the gastrointestinal dysfunctions, which represent evident early manifestations of the disease (Cersosimo *et al.*, 2013).

The most prevalent NMS in PD worldwide are gastrointestinal dysfunction, which includes drooling, nausea, constipation, bloating, prolonged intestinal transit time and delayed gastric emptying (Chaudhuri *et al.*, 2010; Martinez-Martin *et al.*, 2011; Pfeiffer, 2011). The prevalence of these symptoms in patients diagnosed with PD is between 70-80% and precociously condition the quality of life of the patients (Martinez-Martin *et al.*, 2011). The most common symptom among all those mentioned above is constipation, which has an occurrence around 87% of patients with PD and precedes, over a decade, the motor symptoms, which makes it a promising target for treatment due to its large temporal distance from the more severe state of the pathology (Pfeiffer, 2011; Bastide *et al.*, 2015).

Despite the extensive studies carried out, it is not yet clear which factor or factors are responsible for the disease's depletion and which initiates the pathophysiological cascade, it is however very probable that the key factor in the disease's disincentive is an external environmental factor, possibly even ingested in the diet, since the early intestinal involvement in PD development reinforces this assumption (Wirdefeldt *et al.*, 2011; Kieburtz and Wunderle, 2013).

2.1- The microbiota-gut-brain axis

The communication and signalling between the gastrointestinal tract and the brain occurs is a bidirectional pathway that is crucial for maintaining homeostasis and that regulates both hormonal and immunological levels. Perturbation of these systems results in major alterations in the stress-response, GI motility and overall behaviour (Cryan and O'Mahony, 2011).

The signalling behind this axis can be seen an extremely complex and its modulation can affect both, normal healthy state and pathological state. Is composed by the autonomic nervous system (both sympathetic and parasympathetic nervous system), the enteric nervous system and central nervous system as well the neuroimmune and neuroendocrine systems (Figure 5) (Bonaz and Sabate, 2009; Nair *et al.*, 2018).

The bidirectional communication is this axis is ensured by efferent fibres projecting to smooth muscle of the gut and glands and by afferent fibres projecting from the gut to integrative central areas. This network establishes a two way interaction between brain function and GI function that maintain a state of homeostasis (Rhee, Pothoulakis and Mayer, 2009).

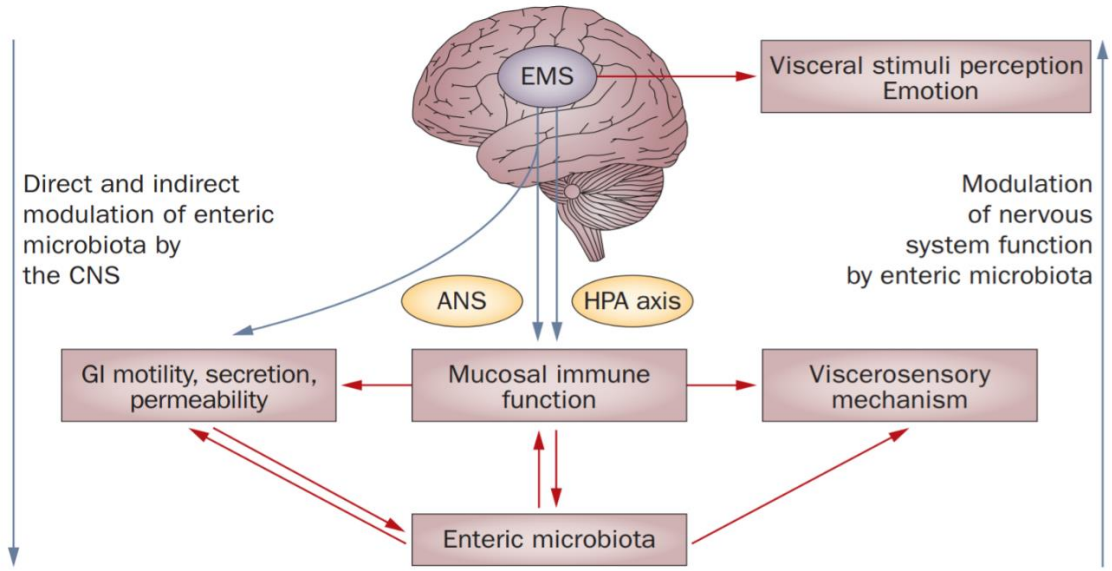

Figure 5- The bidirectional microbiota-gut-brain axis interactions. The emotional motor system (EMS), which include the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis can direct and indirectly modulate the mucosal immune system, thereby modulating GI function and the viscerosensory mechanisms. On the other hand, the enteric microbiota can interact with the efferent neurons, afferent neurons, communicating with the CNS through the parasympathetic and sympathetic nervous systems, thus establishing a bidirectional axis. (Figure adapted from "Principles and clinical implications of the brain–gut–enteric microbiota axis" Rhee, Pothoulakis and Mayer, 2009).

Furthermore, all humans beings have a microbiome in the gut with around 100 trillion microorganisms (Fond *et al.*, 2015), but the great majority of the are present in gut microbiota (Blekhman *et al.*, 2015) which turns out to be one of the most vital parts of our immunity system since they constitute a protective barrier against several harmful factors to our organism. Although most of the microbiome is transmitted by the mother, over the course of life, taking into account factors such as ingested food and the external environment in which it's involved, the microbiome will undergo significant changes so that each human being will have its own unique type of constitution (Bäckhed *et al.*, 2015; Van Opstal and Bordenstein, 2015).

Recent studies confirm that changes in the intestinal microbiota lead to effects on brain activity, since any alteration in the composition of this microbiome creates a cascade of events through the microbiota-gut-brain axis in both physiological and pathological situations, which may be in the origin of several neurodegenerative diseases, in particular in the emergence of PD (Collins, Surette and Bercik, 2012; Cryan and Dinan, 2012; Sampson and Mazmanian, 2015).

2.2- Gut pathology

Recently, several studies carried out in order to identify the origin of PD are oriented to a new perspective, they reveal that the onset of this pathology has its beginning from gut or at least that the gut is intimately involved with its progression and development (Poewe, 2008; Savica *et al.*, 2009).

This new perspective on the disease suggests that some environmental toxin or pathogenic agent is responsible for the onset of the disease, however more prominent studies conducted recent years (Forsythe and Kunze, 2013; Keshavarzian *et al.*, 2015) reveals that the trigger that initiates the pathological process from the intestine does not have to be exclusively of environmental origin, since the intestinal microbiota also has the ability to trigger it (Perez-Pardo *et al.*, 2017). Both environmental microorganisms and those present in the intestinal microbiota, as well as some pesticides that may function as toxins, can cause mucosal inflammation or/and oxidative stress which culminates in α-synuclein accumulation in the ENC (Hawkes, Del Tredici and Braak, 2010).

2.2.1- Dysbiosis in Gut Microbiome

The gut microbiome consists of several types of bacteria, in different proportions but they constitute a microbiome that is in symbiotic equilibrium with the intestine and that helps to preserve the homeostasis.

The microbiota works in conjunction with the host defences and the immune system to protect against colonization and invasion of pathogens (Savage, 1977). It's also responsible for a vital metabolic function, acting as source of essential nutrients and vitamins and helping the extraction of energy and nutrients, in particular short-chain fatty acids (SCFA) and amino acids (AA), from the aliments ingested. When this balance is undone, either by the increase or the decrease of a species proportion, dysbiosis occurs (Carding *et al.*, 2015).

The most frequent causes of dysbiosis are pathogens, hunger, stress, changes in diet, presence of parasites, toxins, drugs and changes in altitude. A diet with excess protein, fat or carbohydrate can cause dysbiosis which results in the production of carcinogenic metabolites that may induce a formation of a neoplasia in the colonic epithelium (Koeth *et al.*, 2013; Carding *et al.*, 2015).

Some bacteria, in particular the species that remain in the mucus layer of the colon establish direct contact with the host cells or, if not in direct contact, may establish an indirect contact through the bacterial metabolites that are received by the cells, in this way they can influence the homeostasis of the host cell, maintaining it or triggering the inflammatory mechanisms of the cell (Carding *et al.*, 2015).

Over the last decade, the connection between dysbiosis and CNS-related disorders has been extensively studied, in the case of PD the most studied is the *Helicobacter pylori*, which is the main responsible for the poor absorption of levodopa, which leads to a less efficient therapy exacerbating the motor symptoms (Çamcı and Oğuz, 2016). These bacteria is associated with small intestine bacterial overgrowth (SIBO), which is an excessive bacterial proliferation and is present in one quarter of all patients diagnosed with PD (Fasano *et al.*, 2013; Tan *et al.*, 2014). Table 1 shows the results of a real-time quantitative PCR performed on fecal samples from patients with PD and in normal individuals where the difference in fecal gut microbiota composition is evident (Nair *et al.,* 2018).

Table 1- Difference in gut microbiota between PD patients and control group. (Table adapted from " Gut Microbiota Dysfunction as Reliable Non-invasive Early Diagnostic Biomarkers in the Pathophysiology of Parkinson's Disease: A Critical Review" Nair *et al.*, 2018).

Bacterial family	Phylum	Change in microbial concentration in PD group compared to control
Prevotellacea	Bacteroidetes	Decrease
Faecalibacterium prausnitzii	Firmicutes	Decrease
Lactobacilli/Enterococci	Firmicutes	Decrease
Akkarmansia muciniphila	Verrucomicrobia	Increase
Bifidobacterium	Actinobacteria	Increase
Methanobrevibacter smithii	Archaea	Increase
Enterobacteriaceae	Proteobacteria	Increase

Although bacteria such as *H. pylori* have a major impact on PD therapy, other types of bacteria have been of interest, namely those belonging to the *prevotellacea* genus. *Prevotella* is a genus of gram-negative bacteria whose main function is to help break down complex carbohydrates into short-chain fatty acids (SCFA) as well as thiamine and folates(Keshavarzian *et al.*, 2015). In people suffering from PD there is clear evidence of a marked decrease in this species of bacteria, as studies published in 2015 (Scheperjans *et al.*, 2015) demonstrate a decrease of more than 77% in fecal samples from PD patients. The decrease in *Prevotellacea* levels causes the decreases of the levels of SCAF and the biosynthesis of thiamine and folate is also diminished (Arumugam *et al.*, 2011). Short-chain fatty acids are the result of metabolic reactions of some bacteria, particularly those involving the degradation of plant polysaccharides (Figure 6).

These fatty acids have anti-inflammatory properties and serves as the main source of energy for colonocytes, they strengthen the barrier of the intestinal mucosa (Gill *et al.*, 2006). Among all SCFAs produced by bacteria, butyrate is the most studied and has important anti-inflammatory properties which are closely linked with the preservation of the intestinal barrier (Cuff, 2004). Through the last years further research indicate that the other two SCFAs, namely acetate and propionate, improve an ongoing inflammatory response in the cellular level and, therefore, acetate and propionate clearly contribute to the anti-inflammatory properties of SCFA (Caricilli, 2014).

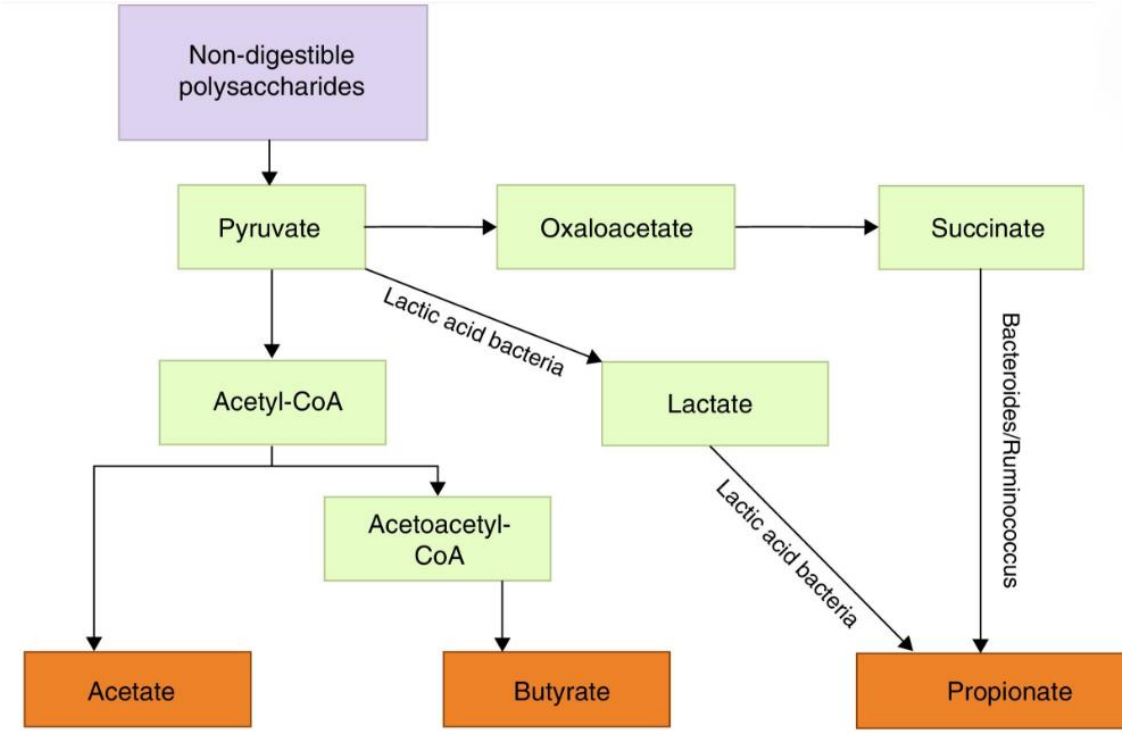

Figure 6 - Scheme illustrating the formation of the 3 main short-chain fatty acids through fermentation of polysaccharides. This crucial steps are mediated by specific kinds of bacteria, since human enzymes cannot metabolize these compounds. (Figure adapted from "Role of intestinal microbiota in the development of multiple sclerosis" Castillo-Álvarez and Marzo-Sola, 2017).

2.2.2- Anti-inflammatory action of short-chain fatty acid

Richard Friedrich Johannes Pfeiffer, a German physician and bacteriologist, was the first to discover the toxic activity of lipopolysaccharides (LPS). These molecules are found in the outer membrane of Gram-negative bacteria, being of vital importance for the structural integrity of the bacteria and are constituted by a lipid and a polysaccharide composed by O-antigen (Parija, 2009).

LPS are classified as endotoxins, which is considered a toxin maintained within the bacterial cell and released only after destruction of the bacterial cell wall unlike the exotoxins, which are released by bacteria in their nearby environment. However, further studies have shown that LPS of gram-negative bacteria does not necessarily require destruction of the bacterial cell wall, they can be secreted from the bacteria as part of their normal physiological activity in the form of vesicles (Kulp and Kuehn, 2012).

Our innate immune system is activated when pattern recognition receptors (PRRs) identify non-specific molecules known as molecular patterns associated with pathogens (PAMPs), which are expressed on the surface of foreign microorganisms.

Toll-like receptors (TLRs) stand out as a particular group of PRRs, they are a family of receptors that recognize specific PAMPs and activate a signal transduction pathway that culminates in an inflammatory response. There are ten TLRs identified in humans, and TLR-4 is responsible for the identification of LPS from Gram-negative bacteria. The TLR-4 pathway is aided by CD4 serum proteins, which present the LPS to one subunit of TLR-4, after that occurs the homodimerization of TLR-4, the process of joining two identical subunits to form a single compound. Through an adapter molecule, myeloid differentiation factor 88 (MyD88) is initiated a complex signalling cascade that ends with the activation of nuclear factor kappa-light-enhancer activated B cells (NF-kB) (Tedelind *et al.*, 2007). NF-kB activation is a result of the phosphorylation of kB inhibitors (IkBs), which are a family of proteins responsible for keeping NF-kB in an inactive state in the cytoplasm, in particular IkBα (Jacobs and Harrison, 1998). The phosphorylation of IkBα leads to its degradation by the release of NF-kB, which is translocated to the nucleus where it reaches its target genes and initiates the transcription of proinflammatory cytokines (Figure 7) (Jacobs and Harrison, 1998).

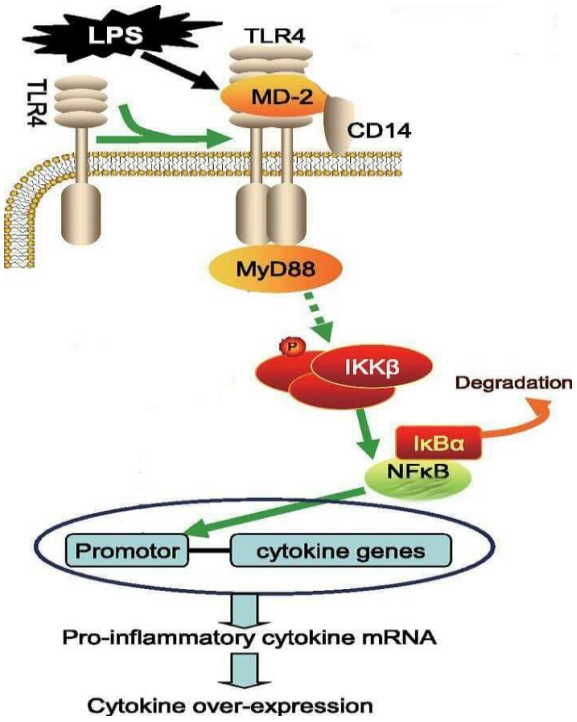

Figure 7- Expression of pro-inflammatory cytokines as a result o TLR-4 activation by LPS. (Figure adapted from" Curcumin attenuates acute inflammatory injury by inhibiting the TLR4/MyD88/NF-κB signaling", Zhu *et al.*, 2014).

The epithelial junctions, which regulate intestinal permeability, are located at the apical end of the intercellular space and are formed by a complex structure composed of different proteins which determine the polarity of the epithelial cells and prevent the free passage of substances representing a barrier to via paracellular. Two major proteins are present in these junctions, claudin and occludin. Although they are fundamental for the integrity of the epithelium, these structures are not static, being highly regulated by cytokines, which modulate the functions of the intestinal barrier in normal physiological state, as well as the ability to deregulate these junctions in pathological situations (Bruewer *et al.*, 2003).

Genes having NF-κB binding sites have been shown to have increased expression, in particular cytokine coding genes, namely, tumour necrosis factor alpha (TNF-α) (Qiu *et al.*, 2004). Overexpression of proinflammatory cytokines, such as interferon gamma (IFN-γ) and TNF-α, induces downregulation of the proteins that make up the junctions, particularly occludin, claudin and zonulin-1 (Gitter *et al.*, 2000). This deregulation leads to an increase in intestinal permeability which consequently induces an increase inflammatory process, once the integrity of the intestinal barrier is lost, with consequently more pathogens penetration through the intestinal epithelium and exacerbating even more the inflammatory response (Perez-Pardo *et al.*, 2017).

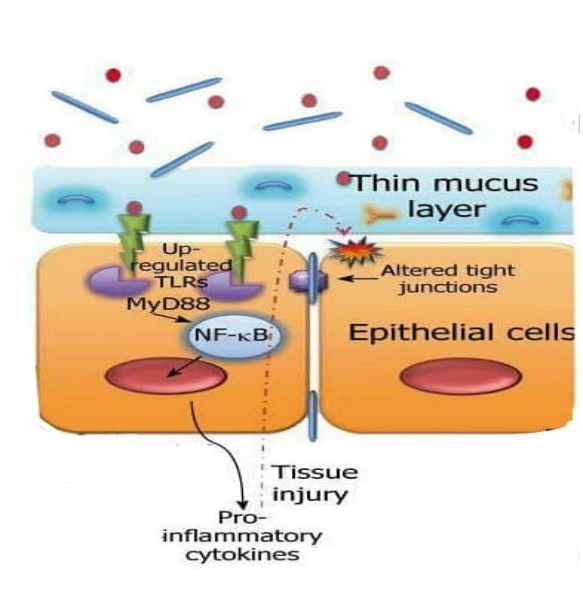

Figure 8- Alteration in the tight junction's integrity due to the activation of TLR. (Figure adapted from "Invasive ability of an Escherichia coli strain isolated from the ileal mucosa of a patient with Crohn's disease" Boudeau *et al.*, 1999).

SCFAs have demonstrated anti-inflammatory capacity in several studies, especially butyrate, which is the most potent of the three major SCFAs. They reveal the ability to supress pro-inflammatory production stimulated by LPS and cytokines, namely TNF-α, NF-κB, IL-6 and NO. The mechanism behind the suppression of these proinflammatory mediators lies in the ability of SCAF to inhibit histone deacetylase (HDCA) activity.

The DNA is wrapped thanks to the action of the histones, which can be acetylated causing the uncoil of DNA or deacetylated causing the compaction of it, being therefore the main mechanism of regulation of gene expression. HDCA and histone acetyltransferases (HATs) are the major enzymes that controls the degree of histone and proteins acetylation (Figure 9). Consequently, the inhibition of HDAC activity by SCFAs significantly increase the acetylation of histone, making the conformation of chromatin more open allowing transcriptional factors and RNA polymerase to interact with DNA to modulate transcription, and causes the acetylation non-histone proteins including NF-κB, thereby modulating gene expression, in this case causing a reduced expression of pro-inflammatory cytokines (Vinolo *et al.*, 2011; Wang *et al.*, 2018).

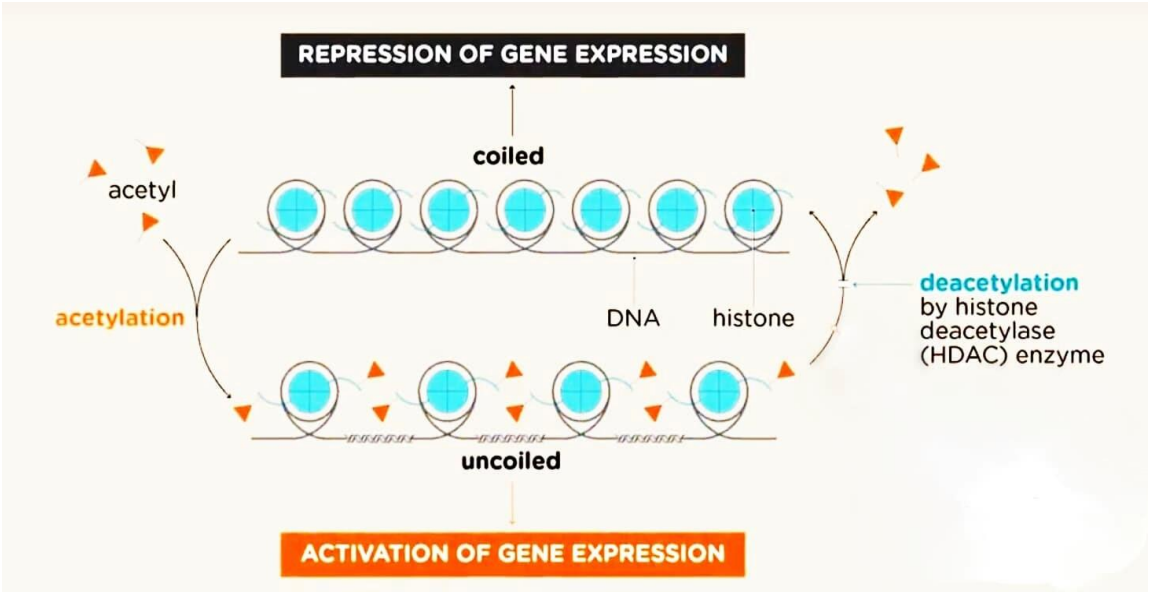

Figure 9- Acetylation and deacetylation of histones mediated by histone acetyltransferases and histone deacetylase, respectively. (Figure adapted from the video "Histone deacetylatse (HDAC) inhibitors" from Myeloma UK, available in the link "https://www.youtube.com/watch?v=OBcpk-M5RYE&t=45s", visited in 27 of July, 2018).

Microglial cells are professional phagocytes present in the central nervous system, being the first and main mechanism of active immune defence. In a healthy state, microglial

cells are considered resting cells, but their processes are very active and constantly research their surroundings to maintain a state of homeostasis and ensure a rapid immune response, preceding any other cell type in the brain (Kreutzberg, 1996).

When in the presence of pathogens, these cells have the ability to produce various inflammatory mediators, releasing neurotoxic factors including nitric oxide (NO) and proinflammatory cytokines, such as TNF-a, constituting the first and fastest CNS immune response against harmful particles, being of microbial origin (as LPS) or result of damaged cells (Park *et al.*, 2005; Filiano *et al.*, 2016). Despite the vital importance of this defence mechanism to preserve the integrity of the CNS, studies in isolated cells and in animal models demonstrate that the chronic or excessive activation of these cells constitutes one of the main mechanisms of neurotoxicity and seems to be involved in the onset and progression of neurodegenerative diseases, with strong evidence pointing to Alzheimer's and Parkinson's disease (Amor *et al.*, 2010; Vinolo *et al.*, 2011).

Although it is still the subject of some controversy, the inhibitory effect of SCFAs on the microglial production of inflammatory mediators reveals in most studies that these fatty acids appear to decrease the activation of microglia or at least minimize their harmful effects on CNS, and the inhibition of HDAC seems to be a determining factor for this decrease. In fact, given the experiences in animal models and the data obtained from them, according to *Kim et al.*, they demonstrate and support the idea that the inhibitory activity of SCFAs and other HDAC inhibitors may be a valuable tool in the treatment of the inflammation of the CNS given its antineuroinflammatory and neuroprotective properties (Kim *et al.*, 2007; Vinolo *et al.*, 2011).

2.2.3- Microglial activation and spreading of α-synuclein

As mentioned before, there are clear evidence that changes in gut bacterial composition leads to an inflammatory response that can spread to the brain.

When dysbiosis occurs in the intestine, which can be caused by a deficient diet or by the ingestion of pathogenic agents to the microbiota population, the loss of certain types of bacteria occurs(Carding *et al.*, 2015). This abrupt loss of species of symbiotic bacteria leads to a decrease in SCFAs and an increase in the concentration of LPS since they are endotoxins and their release is enhanced when lysis of the microorganism occurs. The increase of LPS in turn will stimulate the TLR-4 receptors, which due to the decrease of SCFA will have a more exacerbated anti-inflammatory response than in situations where the microbiota is in

equilibrium (Tedelind *et al.*, 2007; Zhu *et al.*, 2014).The increase in pro-inflammatory factors then causes an excessive reaction within the intestinal mucosa which will lead to destruction of intestinal wall integrity, since these factors affect the proteins responsible for tight junctions, namely claudins and occludins (Gitter *et al.*, 2000). The loss of integrity of the intestinal epithelium allows more pathogens to enter, increasing even more the inflammatory response. The entry of LPS has a major role in the disruption of the of the blood-brain barrier. Although we do not know for sure the mechanism by which the LPS compromise the integrity of the BBB, but already in 1958, Eckman et al. established that there is a relationship between Gram-negative endotoxins and BBB disruption (Banks *et al.*, 2015). Because BBB is sensitive to inflammatory processes, the induction of proinflammatory cytokines and oxidative stress generated by components such as NO increase its permeability, allowing the entry of LPS into ENS (Noworyta-Sokolowska, Górska and Golembiowska, 2013).

Microglial cells are highly sensitive to the presence of LPS, since these are the main and most immediate innate defence line of the CNS, their activation produces a variety of neurotoxic factors. These neurotoxic factors are in a state of homeostasis, but when uncontrolled activation causes damage and cell death. Despite this, damaged neurons can produce signals stimulating the activation of more microglia cells, which eventually becomes a cycle of self-amplification of damaged neurons and microglial activation (Liu and Bing, 2011).

In addition to the propagation of the inflammatory process through the microglia cells, oxidative stress and intestinal inflammation can lead to the formation of α-synuclein aggregates in ENS. The formation of these aggregates will lead to the accumulation of α-synuclein in the ENS which will spread to the vagus nerve, through which it will be propagated from neuron to neuron to reach the CNS (Figure 10). The vagal nerve provides a spreading pathway for α-synuclein from the ENS to the brainstem, midbrain, basal forebrain and to the cortical areas(Forsyth *et al.*, 2011; Perez-Pardo *et al.*, 2017).

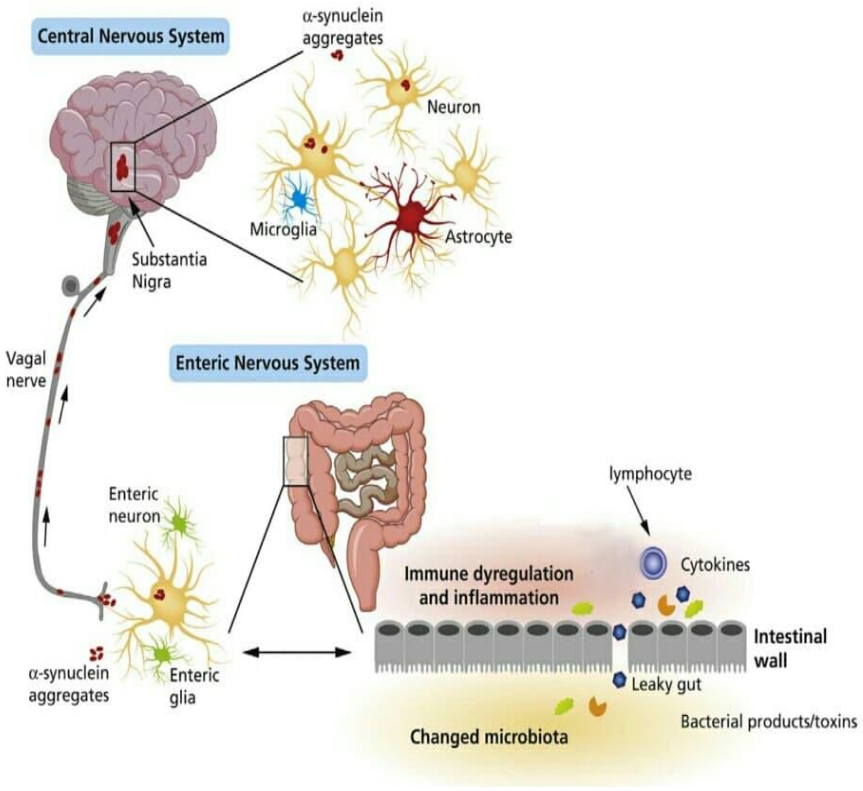

Figure 10- Schematic representation of how changes in microbiota can induce excessive mucosal inflammation, leading to a α-synuclein accumulation in the ENS. The vagal nerve works like a pathway that spread the α-synuclein from the ENS to the CNS. (Figure adapted from" The gut-brain axis in Parkinson's disease: Possibilities for food-based therapies", Perez-Pardo *et al.,* 2017).

3- Food-based therapies targeting the microbiota-gut-brain axis

Current therapeutic options, while offering relief of motor symptoms, do not contribute to regression or to prevent the progression of Parkinson's disease. In addition, most NMS do not respond to dopamine replacement therapy, since a large percentage of NMS is the result of dysfunctions of several neurotransmitters, not only dopamine, thus requiring more effective therapies (Lee and Koh, 2015).

As the administration of antiparkinsonian medication is taken orally, the integrity of the intestinal function is obligatory to obtain an adequate therapeutic response. In addition, several clinical trials converge to the conclusion that the administration of levodopa produces a delayed gastric emptying in healthy individuals (Epprecht *et al.*, 2015), which, in association with the intestinal dysfunction present in patients with PD, can amplify the present symptomatology in the intestine. In addition, levodopa absorption is also impaired due to delayed gastric emptying, causing a lower peak plasma concentration and more exacerbated fluctuations of the on-off periods of the drug (Doi *et al.*, 2012; Marrinan, Emmanuel and Burn, 2014).

Given this perspective, it would be potentially advantageous to study and investigate new strategies focused not only on dopaminergic therapy but also on the treatment of GI dysfunction, which would consequently improve the absorption rate of the drug, reducing the amount of drug required to have effect and minimizing side effects. Since the intestines may play a relevant role in the development of PD, focusing therapy in its dysfunction may open the door to a new approach to NMS, since dopamine replacement therapy alone does not demonstrate ability to attenuate these symptoms considerably (Doi *et al.*, 2012; Perez-Pardo *et al.*, 2017).

In this context, nutrition-based therapies have enormous potential as they can directly affect the gut through precursors of the phospholipid membrane and cofactors, as well as affecting the composition of the microbiota with the help of probiotics, prebiotics and synbiotics. In addition to traditional therapy, this dietary therapy can contribute to the preservation of neuronal function in the ENS and CNS, through the microbiota-intestine-brain axis and, thus, in the progression of the disease itself (Maslowski and MacKay, 2011; Cryan and Dinan, 2012; Clemente *et al.*, 2016).

3.1- Phospholipidic membrane precursors and cofactors

The use of certain membrane precursor compounds and cofactors may reduce neuronal degeneration, notably caused by membrane-related pathology found in CNS and ENS, and these substances have shown beneficial clinical properties in preclinical studies in both motor and non-motor symptomatology (Perez-Pardo *et al.*, 2018).

In recent studies, three phospholipid precursors, uridine, docosahexaenoic acid (DHA) and choline, omega-3 fatty acids, have aroused the scientific community's interest in its synapogenic properties. The combination of these three nutrients accelerates the formation of the synaptic membrane, since these are the main precursors substrates of the components of the synaptic membranes. Synaptogenesis is at its highest peak in the first years of life, since at this time the concentrations of these nutrients are considerably high, which is result of the large amounts of mainly uridine, ingested through mother's milk (Wurtman, 2014; Perez-Pardo *et al.*, 2017). However, as uridine is mainly found in RNA, its bioavailability through food intake is practically insignificant, as well as the low amount of DHA and choline present in the usual diet, which is why the plasma levels of these nutrients are usually low. Since circulation is the main responsibility for the supply of phospholipid precursors, a low plasma concentration of precursors cannot guarantee optimal synaptogenesis in adults (Wurtman, 2014).

Phosphatidylcholine, the major component of biological membranes and other related membrane constituents, requires that the enzymes that catalyse their synthesis have low affinity for their substrate, since the concentrations of uridine, DHA and choline normally found in brain cells are relatively low. It is crucial that these components are not easily catalysed so as not to fall into critical levels of concentration. However, when the concentration of these substrates is increased by the ingestion of these nutrients in the diet, more enzymes responsible for the catalysis of the membrane components are bound to the substrate, despite the low affinity, and consequently more product is synthesized (Wurtman *et al.*, 2009). The use of phospholipid synthesis cofactors, such as vitamin B12, vitamin B6, vitamin C, vitamin E, and selenium, allows a greater bioavailability of the membrane precursors, since they increase their absorption and facilitate the metabolization process (Van Wijk *et al.*, 2014).Theoretically the simultaneous administration of these three precursors with the respective cofactors will cause an increase in the number of phospholipids and synaptic proteins as well as an increase in the density of the dendritic spines and neurite outgrowth as showed in Figure 11 (Sakamoto, Cansev and Wurtman, 2007; Holguin *et al.*, 2008).

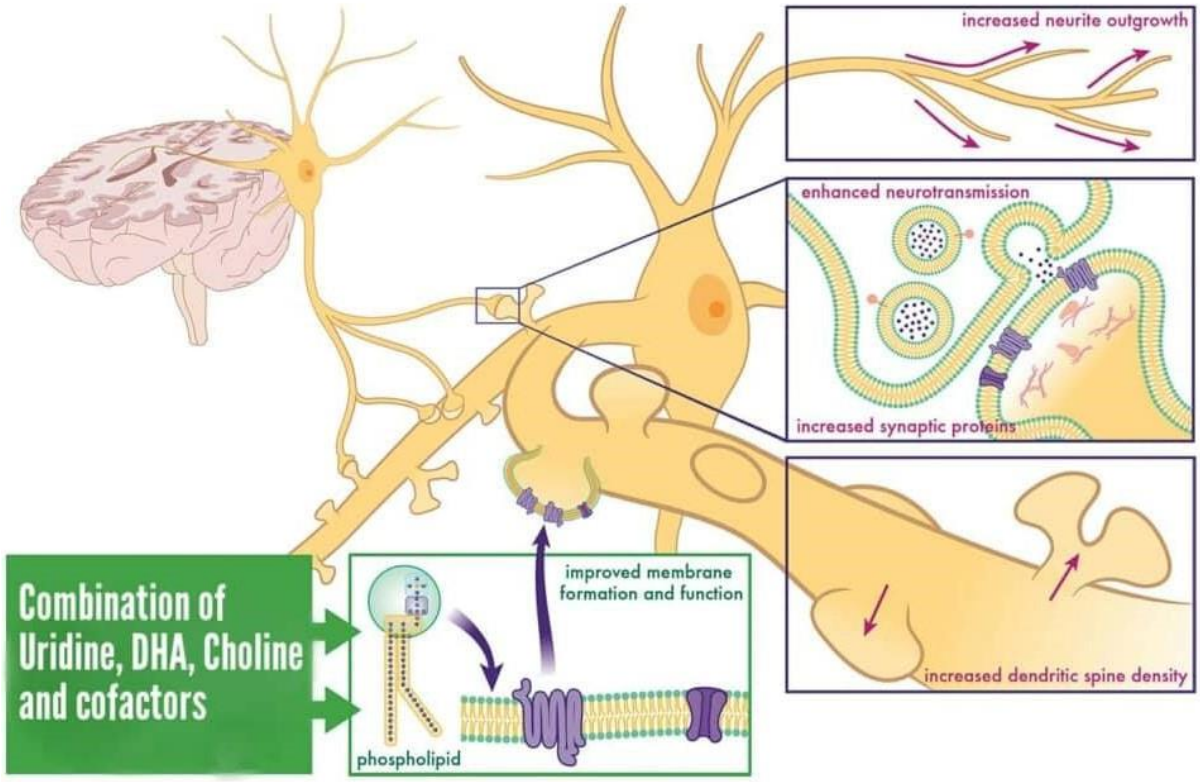

Figure 11- The stimulation of the formation and function of membranes through the administration of uridine, DHA and choline with their cofactors (in green) leads to increased neurite growth, denser dendritic spines and higher levels of pre- and post-synaptic proteins essential for formation of new synapses (in purple). (Figure adapted from "Targeting synaptic dysfunction in Alzheimer's disease by administering a specific nutrient combination", Van Wijk *et al.*, 2014).

The co-administration of uridine, DHA, and choline has revealed in several studies immense potentialities in the treatment of PD. According to Cansev et al., oral administration of a combination of precursors (uridine and DHA) has been shown to restore a considerable percentage of dopaminergic neurotransmission in animal models, which, in theory, could help increase the function of nigrostriatal synapses in PD patients by 15–25% (Cansev *et al.*, 2008). Recent studies have shown that daily fat intake appears to modify the risk of developing PD directly or by altering the mechanism of response to neurotoxins of environmental origin. These studies have evaluated the effects of high levels of polyunsaturated fatty acids (PUFAs) using DHA as a reference, noting that PUFAs have promising anti-inflammatory capabilities and may improve mitochondrial dysfunction. The result of these effects is a reduction of oxidative stress and consequently a decrease in the accumulation of α-synuclein aggregation in the ENS (Miller *et al.*, 2009; Afshordel *et al.*, 2015; Perez-Pardo *et al.*, 2017).

3.2- Probiotics

Probiotics are live bacteria and yeasts, which when ingested in adequate quantities promote various health benefits by restoring the natural balance of bacteria in the intestine (as well as in the stomach) when it is disturbed by disease or by treatment as well as preserving immune homeostasis (Reid *et al.*, 2011). Supplements and foods containing probiotic bacteria are marketed in various everyday products usually in the form of fermented dairy products such as yogurts and beverages, as well as in cereals, thus not requiring a medical order (Varankovich, Nickerson and Korber, 2015).

Currently, the most commonly used bacteria for human ingestion are representative of *Bifidobacterial, Lactobacilli, Enterococci* and yeasts that have shown health benefits, including reduction of pathogenic organisms in the gut, stimulation of the body's immune response and synthesis of several factors antimicrobial agents responsible for controlling the growth of the remaining bacterial species (Ait-Belgnaoui *et al.*, 2012; Varankovich, Nickerson and Korber, 2015). According to studies conducted by Dinan *et al.,* it has been demonstrated that animal models subject to a daily diet of probiotics contribute to the decrease of anxiety states, giving rise to a new term that classifies probiotics with anxiolytic functions as psychobiotics, which is defined as a "living organism which, when ingested in inadequate amounts, produces a health benefit in patients suffering from psychiatric illness" (Dinan, Stanton and Cryan, 2013). These neurological effects caused by the administration of probiotics also prove effective in the functioning of the human brain, proving to ameliorate the cases of depression and anxiety, as well as at the gastrointestinal level can minimize GI dysfunction and increase gastric motility.

Lactic acid bacteria, such as *lactobacilli*, can improve digestion, absorption and availability of nutrients, but also have the capacity to inhibit or kill H. pylori, which due to its excessive proliferation is considered a major cause of gastritis, inflammation intestinal and peptic ulcers(Rao *et al.*, 2009; Zaharoni *et al.*, 2011).

Bifidobacteria constitute a important percentage of the human microbiota, they Gram-positive, non-motile anaerobic bacteria that are responsible for the metabolization of dietary carbohydrates that are not digestible by the host, among them the prebiotics, whose metabolites are responsible for stimulating the growth of specific species of benign bacteria in intestinal homeostasis. In addition, they demonstrated the ability to inhibit enteropathogenic adherence of enterotoxigenic E. coli and E. coli to intestinal epithelial cells, which are bacteria present in the intestine, but which can cause viral infections. This inhibition of adhesion caused by *Bifidobacteria* allows the prevention or relief of infectious diarrhea and reduces the symptoms of inflammation of the intestine (Gomes and Malcata, 1999; Sanz, 2007; Flint *et al.*, 2012).

Despite the numerous advantages offered by probiotics, the studies conducted in its use in the treatment of PD are still insufficient and limited, since only its isolated use does not guarantee a sufficiently effective therapy. However, its use in complementarity with conventional antiparkinsonian drugs allows a greater therapeutic efficacy, since they improve the intestinal function, decrease the intestinal permeability and consequently the neuronal inflammation caused in the ENS, as well as increase the absorption of levodopa, since probiotics maintains the balance of the intestinal microbiota (Liang *et al.*, 2015; Perez-Pardo *et al.*, 2017).

3.3- Prebiotics

According to Gibson and Roberfroid, a prebiotic is a 'non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and / or activity of one or a number of bacteria in the colon, and thus improves host health' (Gibson and Roberfroid, 1995). They are dietary oligosaccharides that cannot be metabolized by human enzymes, have resistance to gastric acids, are not hydrolysed and cannot be absorbed, being fermented only by the intestinal microbiota. Although prebiotics are oligosaccharides, not all oligosaccharides are prebiotics, they are only considered as such if they exhibit the above-mentioned characteristics, but they also must specifically stimulate the growth of bacteria with beneficial capabilities for the organism (Gibson *et al.*, 2004).

Two oligosaccharides, fructo-oligosaccharide (GOS) and fructo-oligosaccharide (FOS), are formed from fructose and lactose, respectively, reaching the colon without practically any type of metabolic alteration in its structure. Once in the colon, they are fermented by specific strains of Bifidobacteria, whose metabolites include SCFA, carbon dioxide, methane, hydrogen and lactose. These metabolites have a detrimental effect on pathogenic bacteria and prevent their proliferation, since these metabolites acidify the colon (Patel and Goyal, 2011).

Despite the evidence revealed in recent years on the various beneficial effects of prebiotics on brain function and their neuroprotection, as well as their relevant role in the maintenance of microbiota homeostasis and in the treatment of GI dysfunction, trials have not yet been performed on its use in of PD. But as noted above, the reduction of SCFA in PD patients suggests strong evidence of the potential contribution of prebiotics in a therapy supplemented also by probiotics (Keshavarzian *et al.*, 2015; Unger *et al.*, 2016; Perez-Pardo *et al.*, 2017).

3.4- Synbiotics

When a product has probiotics in its composition and prebiotics is simultaneously designated as synbiotics. However, the term symbiotic is unique to products in which the prebiotic specifically favours the probiotics contained in the formulation, since the word alludes to the synergy between the two (Schrezenmeir and Vrese, 2001). The combination of probiotics and prebiotics greatly enhances their beneficial effects on health by promoting a better intestinal barrier function, increasing the amount of beneficial intestinal microbes, as well as hindering the growth and proliferation of several Gram-negative pathogens, reducing the leakage of LPS and leading to proinflammatory decrease and, consequently, a decrease in the production of cytokines(Rajkumar *et al.*, 2015).

As previously mentioned, SIBO is present in the great majority of diagnosed cases of PD, and has great influence not only in the reduction of levodopa absorption, thus worsening the fluctuations of the drug and thus aggravating the motor symptoms, as well as in the increase of intestinal inflammation (Tan *et al.*, 2014). However, clinical trials in patients diagnosed with SIBO who received antibiotics and later synbiotics showed promising results with a considerable reduction of SIBO compared to patients treated with probiotics or prebiotics alone (Khalighi *et al.*, 2014).

These results reinforce the idea that a correct supplementation of combined probiotics and prebiotics may contribute to a more effective therapy in the treatment of PD. It is possible not only to reduce motor symptoms, but also to ameliorate NMS (Perez-Pardo *et al.*, 2017).

4- Conclusion

To the present day there is no cure or treatment to prevent the progression of sporadic PD, and although it is possible to reduce its motor symptoms, the disease itself remains one of the main challenges of modern medicine.

Recent studies have opening new biomedical avenues for the treatment of PD by showing a complex and dynamic connection between the brain and the gut, a communication pathway that was thought irrelevant two decades ago by the scientific community. This new perspective on how events in the gut can induce pathologies that can propagate to the brain has raised an increasing interest in the study and elucidation of the physiological mechanisms associated with this bidirectional axis. Studies to this date converge in the sense that intestinal inflammation may be at the origin or strongly contribute to the development of PD and is therefore one of the most promising therapeutic targets that could stopping progression and reducing NMS. Given that the mechanism of some inflammatory processes associated with intestinal dysfunction is already adequately elucidated, many of which seem to be related to imbalances of the microbiota, it is therefore relevant to look for ways to decrease or reverse the inflammation caused. This intervention may involve probiotics, prebiotics, membrane precursors and synbiotics as they reveal considerable anti-inflammatory as well as neuroprotective properties.

Despite all the studies conducted in this area, the information is still insufficient to define a completely effective therapeutic that allows alternatives to conventional therapy, yet the neuroprotection and anti-inflammatory properties of an improved microbiota described in several scientific works, promises to open horizons to a new paradigm in the treatment not only of PD as of other neurodegenerative diseases.

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Relatório de Estágio em Farmácia Comunitária

Orientado pelo Dr. Orlando António Gonçalves Fernandes, na Farmácia Gonçalves.

Conteúdo

LISTA DE ABREVIATURAS

MICF - Mestrado Integrado em Ciências Farmacêuticas

SWOT - *Strenghts, Weaknesses, Opportunities and Threats*

Introdução

No atual plano do Mestrado Integrado em Ciências Farmacêuticas (MICF) está integrada a realização de um estágio em Farmácia Comunitária no segundo semestre do quinto ano, sendo este de caracter obrigatório o meu estágio foi realizado na Farmácia Gonçalves, em Melgaço, entre o dia 8 de Janeiro e o dia 10 de Maio de 2018, sob orientação do Dr. Orlando António Fernandes Gonçalves.

Durante o meu percurso no curso de MICF, adquiri ao longo de cinco anos diversos conhecimentos práticos e teóricos nas diversas vertentes da área farmacêutica, permitindo-me este estágio pôr em prática todos estes anos de estudo, podendo aplicar tudo o que me foi lecionado e enfrentar de modo correto todas as situações da prática profissional. Hoje em dia a Farmácia Comunitária pode ser considerada a vertente mais visível da profissão, uma vez que está é o local que os utentes procuram primeiro, não só para dispensa de medicamentos, mas também para receberem aconselhamento e encontrarem resposta as mais diversas questões de saúde, tornando o papel do farmacêutico cada vez mais importante na defesa e promoção da saúde. Podemos desta forma considerar a prática de Farmácia Comunitária como um dos pilares base de um sistema de saúde eficiente e de qualidade, permitindo dar resposta rápida e adequada aos cuidados de saúde primários, transparecendo para o utente uma imagem de segurança, disponibilidade e confiança.

1- Contextualização da Farmácia

Farmácia Gonçalves

A Farmácia Gonçalves localiza-se no concelho de Melgaço, pertencente ao distrito de Viana do Castelo, cuja direção técnica está ao cargo do Dr. Orlando Gonçalves.

Foi a farmácia de eleição pessoal para a realização do meu Estágio Curricular em Farmácia Comunitária durante os meses de Janeiro a Junho de 2018 (duração de 6 meses), uma vez que já tinha realizado estágio extracurricular lá durante os meses de Julho e Agosto de 2017. Para além de se encontrar perto da minha área de residência, a Farmácia Gonçalves conta com uma equipa jovem e dinâmica, a qual me apresentou uma formação completa e rigorosa, mas também um forte espírito de equipa e colaboração, facilitando imenso a minha integração e acompanhando sempre o meu percurso.

O horário de funcionamento semanal decorria de Segunda-Feira a Sexta-Feira das 8:30 às 20:30, estando também de serviço ao Sábado, das 9:00 as 19:30, e ao Domingo, das 10:00 às 12:30 e das 14:30 as 19:30.

2- Análise SWOT

Uma análise SWOT é uma ferramenta muito utilizada em diversas áreas e a qual permite elaborar um diagnóstico estratégico da empresa, mas devido a sua simplicidade, pode facilmente ser utilizada para qualquer tipo de análise de cenário, sendo que neste caso é utlizada de modo a avaliar o meu percurso ao longo do meu estágio.

Pretende ser uma análise com uma vertente mais pessoal, baseada nas experiências vividas durante o meu estágio curricular, permitindo-me avaliar de forma simplificada os aspetos positivos e negativos deste .Esta análise divide-se em duas vertentes, sendo uma delas uma vertente mais interna, a qual analisa os pontos fortes (Strenghts) e dos pontos fracos (Weaknesses) e por uma vertente mais externa, através da avaliação de oportunidades (Opportunities) e de ameaças (Threats).

Pontos Fortes	**Pontos Fracos**
• Equipa Técnica • Interação Farmacêutico-utente • CashGuard • Consultas de Nutrição e Podologia • Protocolos de Fornecimento a instituições e empresas • Conferência do Receituário	• Dermocosmética • Preparação de Manipulados
Oportunidades	**Ameaças**
• Grande zona de estacionamento • Remodelação da farmácia	• Existência de Farmácias circundantes • Adesão do Utente a Medicamentos Genéricos • Barreira Linguística

3- Pontos Fortes

3.1- Equipa técnica

A equipa técnica da Farmácia Gonçalves é formada por uma técnica de farmácia, três farmacêuticas e pelo diretor, o qual está sempre presente na farmácia e avalia constantemente

a dinâmica da equipa de modo a potenciar as capacidades individuais de cada membro.

É uma equipa jovem mas extremamente profissional que desde o primeiro dia facilitou a minha integração e sempre se mostraram disponíveis para me auxiliar nas diversas tarefas que realizei. Dado que era o único estagiário, recebi total atenção e apoio por parte de todos os membros da equipa, o que foi imensamente enriquecedor para o meu processo de aprendizagem uma vez que sempre me foi exigido o máximo rigor e compromisso com a atividade profissional. Durante os primeiros dias de atendimento ao utente tive sempre a ajuda de um membro da equipa, auxiliando-me nas indecisões que surgiam durante o aconselhamento ou na resolução de problemas na utilização do sistema informático. Acompanhei também muitos dos atendimentos prestados pelos membros da equipa técnica de modo a integrar bases mais solidas sobre o melhor aconselhamento em situações práticas, permitindo familiarizar-me com diversas referências de produtos e diferentes abordagens, podendo assim oferecer ao utente mais opções de tratamento.

A oportunidade de trabalhar com um grupo tão dinâmico e com um forte espírito de cooperação foi sem dúvida um dos pontos mais fortes do meu estágio, pois para além de toda a experiência que me foi transmitida, sempre me senti apoiado e completamente integrado. O facto de fazer parte de uma equipa tao funcional fortaleceu a minha confiança para lidar com os desafios que este estágio me proporcionou e permitiu-me desenvolver rapidamente tarefas mais exigentes.

3.2- Interação Farmacêutico-Utente

Sendo que a Farmácia Comunitária é a área que mais explora a interação farmacêutico-utente, exige por parte dos profissionais em saúde respostas rápidas, claras e corretas as mais diversas questões impostas pelos utentes, fazendo do atendimento um desafio gratificante aos conhecimentos por mim adquiridos durante o meu percurso em MICF.

Durante o meu estágio tive imensa formação na prática de atendimento, uma vez que diariamente estava ao balcão. Inicialmente senti alguma insegurança na realização de atendimentos devido a minha falta de experiência, temendo que qualquer erro da minha parte se repercutisse em problemas para a saúde e bem-estar do utente ou mesmo para a imagem da farmácia. Durante esse período tive sempre a cautela de pedir ajuda a qualquer um dos membros da equipa técnica os quais estavam sempre disponíveis para me auxiliar em qualquer situação e me incentivavam a enfrentar os meus receios. Esse apoio foi essencial para ultrapassar os meus medos e gradualmente aumentar a confiança no meu trabalho. Outro

facto importante foi a elevada afluência de utentes a Farmácia Gonçalves, o qual me permitiu lidar com diversas situações de aconselhamento farmacêutico como também de esclarecimento de dúvidas sobre a medicação e tratamento que os utentes estavam a seguir. Isto ajudou a desenvolver a minha autonomia e confiança na tomada de decisões, melhorando a minha capacidade de resposta aos diversos casos que me foram surgindo bem como a minha destreza na resolução de problemas.

Para além da aplicação pratica de todos os conhecimentos por mim adquiridos, o intenso contacto com o publico permitiu desenvolver as minhas capacidades de comunicação, oferecendo assim um atendimento mais personalizado e diferenciados, criando uma relação de maior proximidade e acompanhamento com o utente.

3.3- Utilização do Sifarma 2000®

A Farmácia Gonçalves aptou pela utilização do Sifarma 2000® que é um software de gestão e organização desenvolvido pela Glintt®, sendo este uma ferramenta de trabalho essencial no quotidiano de uma farmácia.

É um software é caracterizado pela sua facilidade de utilização e pelas inúmeras funções e procedimentos o que permite a múltipla execução de tarefas, fazendo a gestão do produto desde a entrada até a saída, gerando informações organizadas e detalhadas sobre cada medicamento, permitindo um controlo de stock, gestão dos prazos de validade e etiquetagem. Permite também a leitura de receitas medicas eletrónicas com grande rapidez, sendo também possível fazer o acompanhamento do histórico do doente aumentando assim a proximidade com este.

Como estagiário senti que o Sifarma 2000 foi uma mais valia para a minha formação, uma vez que este programa disponibiliza toda a informação sobre os medicamentos inseridos na base de dados, permitindo-me oferecer aconselhamentos mais precisos e corretos, podendo ainda alertar o utente para possíveis efeitos secundários e evitando interações medicamentosas.

3.4- CashGuard®

O CashGuard® é um equipamento de gestão e manuseamento automático de numerário. A utilização desta ferramenta de trabalho em Farmácia comunitária tem como principais vantagens a poupança de tempo e a segurança, dado que este sistema faz trocos muito rapidamente, eliminando erros humanos na altura do pagamento, e conta com um

sofisticado sistema antirroubo.

Durante o meu estágio recebi formação por parte diretor técnico sobre a utilização deste equipamento, explicando-me como funciona, como repor a falta de notas ou moedas e ainda como proceder em caso de falha do sistema. Pessoalmente facilitou imenso os meus atendimentos graças a rapidez com que o pagamento era realizado e pela salvaguarda oferecida pelo equipamento na correta devolução do troco, o que me permitia dar mais atenção ao utente no final da dispensa dos medicamentos.

Embora os trocos fossem gerados automaticamente, sempre verifiquei se o valor efetivamente coincidia com a diferença a devolver ao utente, minimizando assim a margem de erro.

3.5- Consultas de Nutrição e Podologia

Esta farmácia dispõe de consultas de nutrição, sendo estas semanais, como também dispõe de consultas de podologia as quais se realizam mensalmente.

Relativamente as consultas de nutrição, a primeira consulta era mais longa, demorando por volta de trinta minutos, realizando um questionário detalhado do utente sobre a sua idade, os seus hábitos de vida, bem como informações sobre a história clínica deste e sobre os seus hábitos alimentares. Posteriormente o nutricionista procedia a realização de diversas medições de avaliação corporal, como o peso, a altura, cálculo do índice de massa corporal, a percentagem de massa gorda e a medida do perímetro abdominal. Após a analise de toda esta informação, o nutricionista determinava quais os parâmetros na alimentação que necessitavam de ser alterados, tendo em conta os objetivos pretendidos pelo doente, tendo sempre em conta a prevenção de doenças e evitando défices alimentares. Era apresentado ao utente um plano de alimentação onde estava definido um valor calórico diário, bem como conselhos referentes a pratica exercício físico complementar à dieta. Após a primeira consulta, semanalmente o utente terá sessões mais curtas com o nutricionista, consultas com por volta de 15 minutos, onde serão avaliados os resultados do plano estipulado e caso necessário reformular alguns parâmetros do mesmo. Assim que o utente atingisse os resultados pretendidos, era estabelecido pelo nutricionista um plano de manutenção de forma a preservar os objetivos atingidos.

Os serviços de podologia prestados pela Farmácia Gonçalves eram prestados mensalmente através de consultas realizadas por um podologista com marcação prévia. Estas consultas visavam a prevenção, diagnóstico e tratamento das alterações incidentes no pé e nas

suas repercussões no organismo. A área de intervenção das consultas realizadas na farmácia era o Pé de Risco, que visa o tratamento do Pé Diabético. Dentro das diversas situações de Pé de Risco, o Pé Diabético surge como a mais comum, sendo que as alterações inerentes à doença, as quais condicionam o aporte sanguíneo e promovem modificações degenerativas dos pés, afetam a capacidade de lutar contra as infeções. A duração destas consultas era de trinta minutos, onde apos os tratamentos eram também aconselhados produtos de modo a manter a terapêutica até a próxima consulta.

Este tipo de serviços demostra ser extramente benéfico para os utentes, nos quais a apreciava imensa satisfação pelos resultados obtidos e pela comodidade oferecida, uma vez que estas consultas eram realizadas no próprio espaço da farmácia, o que se repercute num maior número de fidelizações.

3.6- Protocolos de Fornecimento a Instituições

No concelho de Melgaço existem diversas intuições, maioritariamente lares de idosos, os quais tem parceria com a Farmácia Gonçalves para o fornecimento da medicação assim que requerida.

Dado que estas instituições necessitam de ter em stock diversos medicamentos para uso dos utentes lá ingressados, é importante que a farmácia se responsabilize por uma rápida dispensa destes mesmo medicamento de modo a suprimir as necessidades destas instituições. Como tal durante o meu estágio pude processar vários pedidos de medicação enviados por lares não só do concelho como também de concelhos vizinhos. O pedido de medicação é feito sob a forma de e-mail, o qual era enviado para o correio eletrónico da farmácia, ou caso o pedido não fosse superior a vinte medicamentos poderia ser realizado por chamada telefónica. A razão pela qual o número limite de medicamentos era vinte por chamada telefónica deve-se a uma imposição por parte da direção técnica, de modo a salvaguardar possíveis erros durante o procedimento do pedido, uma vez que era feito por chamada telefónica e implicava que o profissional que a recebeu anota-se os medicamentos pedidos, o que poderia causar erros quer seja pelo nome do medicamento ou pela dosagem.

Após receção do pedido este era imediatamente processado estando a encomenda pronta no próprio dia em que foi feito o pedido, exceto quando o pedido era realizado durante o fim da tarde e a farmácia não dispunha de algum dos medicamentos requerido. Nesse caso o medicamento era encomendado nessa mesma tarde e a encomenda estaria pronta na manhã seguinte.

Esta rápida resposta no fornecimento da medicação é sem dúvida um dos pontos fortes da farmácia, uma vez que assegura a rápida reposição dos stocks dos lares e dado a existência de um protocolo entre ambas permite as instituições beneficiarem de descontos na aquisição de grandes volumes de medicação. A nível pessoal foi importante para a minha formação, uma vez que foi das primeiras tarefas que realizei e que me permitiu conhecer e manusear o sistema informático de modo que quando comecei a realizar atendimentos me sentia a vontade com utilização deste. Para além de dominar melhor o sistema informático também entrei em contacto com as receitas enviadas, conhecendo assim os diversos formatos de receita e quais os parâmetros a ter em conta para confirmar a sua validade.

3.7- Conferência de receituário

A verificação do receituário é efetuada diariamente por um dos colaboradores da equipa técnica, sendo está tarefa de extrema importância e responsabilidade, uma vez que é crucial que todas a receitas sejam enviadas em conformidade com aquilo que é legalmente exigido para que seja devolvido o valor da comparticipação.

Ainda ao balcão, durante o atendimento e logo a seguir à dispensa, as receitas dispensadas devem ser verificadas atentamente, confirmando que se encontravam dentro do prazo de validade, apresentavam assinatura do médico prescritor bem como a vinheta do médico e do local de prescrição, o número de beneficiário do utente, a faturação da receita com o devido organismo, data da dispensa e assinatura do responsável pela mesma e ainda confirmar se a assinatura do utente se encontrava no local apropriado. É também necessário confirmar se os medicamentos dispensados estão de acordo com a prescrição, tendo especial as quantidades, a forma farmacêutica e as dosagens prescritas na receita. Qualquer erro detetado na verificação técnica do receituário deve ser imediatamente corrigido, devendo separar-se e identificar as receitas que necessitam de ser corrigidas e providenciar a sua retificação junto do doente, médico ou organismo, conforme aplicável. Após verificar se as receitas estão datadas, carimbadas e rubricadas pelo responsável da dispensa, estas devem ser rubricadas no canto superior direito, pelo responsável pela sua verificação, para evidenciar que estão em conformidade. Posteriormente as receitas são separadas em lotes de 30 receitas, arrumadas sequencialmente por organismo e por mês, os quais serão envidos as entidades responsáveis pela comparticipação.

Tive oportunidade de realizar esta tarefa a qual exigiu de mim máxima responsabilidade e atenção, uma vez que é um processo fundamental para a estabilidade financeira da farmácia visando sempre evitar a devolução de receitas de modo a garantir a atribuição do valor da

comparticipação por parte do organismo responsável.

4- Pontos Fracos

4.1- Dermocosmética

Apesar de ter recebido formação em dermocosmética durante o meu percurso em MICF, senti que os conteúdos lecionados não se adequam totalmente as necessidades exigidas pela prática profissional, pelo que não me senti a vontade no aconselhamento desta área.

Dadas as dificuldades que senti, sempre que possível pedia ajuda ou acompanhava algum membro da equipa técnica durante os seus atendimentos, o que me permitiu familiarizar-me com as diversas marcas e gamas de produtos de dermocosmética. Recebi também sessões de formação, realizadas por algumas marcas, bem como esclarecimentos referentes a diversos produtos por parte de delegados de informação medica, enriquecendo assim os meus conhecimentos nesta e permitindo-me realizar aconselhamentos mais completos e diversificados, muitas vezes conseguido realizar vendas cruzadas de produtos complementares.

Embora a minha experiencia inicial fosse um pouco deficitária nas primeiras semanas para me sentir confiante na recomendação de um produto, rapidamente me adequei as necessidades exigidas, em parte graças a vasta gama de dermocosmética oferecida pela Farmácia Gonçalves e a intensa motivação e apoio por parte da equipa técnica, procurando sempre aprofundar dos meus conhecimentos de modo a proporcionar um serviço de qualidade.

4.2- Preparação de manipulados

Durante o meu estágio, observei que um dos pontos mais fracos foi o facto de a Farmácia Gonçalves não preparar medicamentos manipulados e por isso não tive contacto direto com a realização de processos galénicos e de formulação.

Embora a utilização de medicamentos manipulados seja relativamente grande a nível nacional, a realidade é que em meios pequenos, como vilas e aldeias, a procura deste tipo de medicação é reduzida. Dado que a Farmácia Gonçalves se situa num concelho com por volta de dez mil habitantes não se justificaria a preparação de medicamentos manipulados por esta, uma vez que a baixa procura deste não seria sustentável para acarretar os custos subjacentes a aquisição de matérias primas, os quais são elevados, tendo ainda em conta que maiorias a maioria destas matérias primas não seria utilizadas dentro dos seus prazos de validade aconselhados. Contudo, apesar de não ter contacto direto com a preparação de manipulados,

pude realizar os pedidos de preparação a outras farmácias com maior volume de preparações. O pedido era realizado por fax onde eram discriminados os componentes e quantidades de cada manipulado.

Apesar de ter sido um dos pontos fracos do meu estágio, compreendo que é necessário que cada farmácia tenha uma gestão personalizada, adequando-se as necessidades subjacentes aos cuidados de saúde da população em que está inserida, oferecendo sempre reposta a todas as exigências, mas preservando também a sua estabilidade financeira.

5- Oportunidades

5.1- Grande zona de estacionamento

A Farmácia Gonçalves dispõe de um grande parque de estacionamento, tendo 12 lugares disponíveis sendo que dois deles são de uso restrito a utentes da farmácia, permitindo uma fácil acessibilidade em qualquer hora do dia.

Este fator é uma importante vantagem em relação as restantes duas farmácias do concelho, uma vez que tem mais do que o dobro de lugares de estacionamento que as outras duas farmácias. A grande acessibilidade dai resultante repercute-se no elevado numero de utentes que frequenta a farmácia, tanto fidelizados como ocasionais, não só pelo fácil e próximo estacionamento oferecido mas também pelo facto de se localizar numa das principais e mais movimentadas vias de acesso a vila.

5.2- Remodelação da farmácia

Manter a estética e funcionalidade de uma farmácia atualizada é fundamental para a diferenciar e destacar das restantes, o que apesar de ser dispendioso devido ao investimento, acaba por se expressar num aumento da afluência de utentes.

Durante o meu período de estágio pude assistir a planificação das novas modificações da Farmácia Gonçalves. Esta planificação não aumentou ou diminui nenhuma área da farmácia, foi apenas uma alteração da estética interior, na qual pude acompanhar o processo de decisão do diretor técnico, o qual muitas vezes me pedia sugestões ou opiniões sobre o projeto.

Após finalizadas as obras de remodelação foi necessário reorganizar todos os produtos expostos, sendo que me foi atribuída a responsabilidade de organizar vários lineares e gôndolas segundo os meus conhecimentos de marketing. Foi exigente e desafiante, mas senti-me a vontade na realização da tarefa graças as bases de marketing que me foram lecionadas no

MICF. Foram criadas novas zonas quentes, onde coloquei em exposição os produtos que necessitam maior visibilidade, e pude também organizar os produtos sazonais antes do início da época de verão.

Todo este contacto com a reorganização da estética da farmácia e com a organização de produtos expostos foi muito gratificante, permitindo-me aplicar e aumentar os meus conhecimentos de marketing.

6- Ameaças

6.1- Existência de Farmácias circundantes

Tendo em conta que o concelho de Melgaço tem em funcionamento três farmácias bem como duas parafarmácias, isto apresenta-se como um potencial ameaça subsistência da Farmácia Gonçalves dada a elevada oferta para um meio pequeno.

Apesar da elevada concorrência no sector, é possível contornar este problema através de uma diferenciação em relação as restantes farmácias. Esta diferenciação é atingida de diversas formas, nomeadamente através da promoção e divulgação, por parte da farmácia, de serviços de interesse para o utente, como também através de promoções e descontos, principalmente em dermocosmética, mas principalmente por um atendimento de excelência, procurando criar uma relação de proximidade e confiança com o utente que o incentive a regressar e se possível fidelizar com a farmácia. Para além destas iniciativas, a Farmácia Gonçalves conta com um programa de cartão de pontos, cartão o qual é oferecido a qualquer utente que fidelizar com a farmácia. Este cartão permite no final de cada compra acumular pontos no cartão do utente, sendo que quando atingir determinado número de pontos o utente pode convertê-los em descontos na aquisição de medicamentos ou outros produtos dispensados pela farmácia. A implementação deste programa de pontos não só aumentou o número de fidelizados como também o número de vezes que o utente vem a farmácia por semana.

6.2- Adesão do Utente a Medicamentos Genérico

Um dos principais desafios que enfrentei durante o meu atendimento ao público foi a forte rejeição de muitos utentes a utilização de medicamentos genéricos, maioria dos quais apresentavam argumentos errados e demonstravam profunda falta de conhecimento sobre o que eram este tipo de medicação.

A exceção de alguns medicamentos, sobre os quais a marca ainda tem licença de

exclusividade comercial, visto ainda estarem dentro do período de patente, a grande maioria dos medicamentos já dispõe do seu respetivo genérico. Em diversas ocasiões fui confrontado com o elevado valor de determinados medicamentos, sendo que sempre informei que tem como alternativa a utilização de medicamentos genéricos, os quais são intercambiáveis com o medicamento original, e o qual apresenta um preço inferior. A grande maioria dos utentes ficava então com duvidas quanto a eficácia e segurança destes medicamentos, visto que se ambos os medicamentos tinham o mesmo efeito não entendiam a diferença de preços. Nesses casos eu passava a dar uma breve explicação sobre o que são medicamentos genéricos, elucidando-os que estes medicamentos obrigatoriamente tem o mesmo princípio ativo e dosagem que o medicamento de referência e para além disso devem demonstrar bioequivalência. Contudo a grande maioria permanecia desconfiada e reticente na utilização de genéricos, tornando muitas vezes complicada a dispensa de medicação quando o medicamento de referência estava esgotado e eu sugeria a escolha de um genérico.

6.3- Barreira Linguística

Uma das áreas fortes na economia do concelho de Melgaço é o sector do turismo, sendo que é uma vila muito visitada por turistas, não só do território nacional como também do estrangeiro. Para alem da vertente turística, apresenta também uma elevada taxa de emigração nomeadamente para França. Dado que muitos emigrantes voltam de férias para Portugal, senti imensas dificuldades em realizar atendimentos quando o cliente não falava português ou inglês. Sendo que maioria dos turistas provinham de França era muitas vezes difícil compreender o que necessitavam, uma vez que os meus conhecimentos de língua francesa são muito reduzidos. Contudo dispúnhamos de um membro da equipa técnica que tinha completa fluidez na utilização da língua francesa, ao qual diversas vezes pedi ajuda durante os meus atendimentos, facilitando assim a dispensa.

Também pude usufruir de pequenas formações por parte deste colaborador no sentido de desenvolver dos meus conhecimentos da língua francesa, permitindo-me numa etapa final compreender melhor o que me era pedido e ganhado assim mais autonomia nestes atendimentos.

7-Casos Clínicos

7.1-Caso 1

Uma senhora de 32 anos dirige-se à farmácia afirmando ter uma tosse intensa e com expetoração, dor de garganta e nariz entupido, sintomas estes que se prologavam há 3 dias. Solicitou-me algum medicamento que fosse eficaz no alívio destes sintomas pois acreditava ser uma constipação. Antes de mais perguntei se sentia dores de cabeça, ao que me referiu que embora não fossem constastes por vezes sentia dores intensas de cabeça e também corporais. Com esta informação procedi a esclarecer o doente que se poderia tratar de uma gripe e não de uma constipação, mas que necessitaria de lhe medir a febre para ter a certeza. O utente aceitou e com o auxílio de um termómetro digital obtive um resultado de 38,7ºC, o que me permitiu confirmar que o doente estava com gripe. Expliquei então que a gripe é causada por um vírus da família *Influeza*, sendo que os sintomas da gripe são em geral mais severos que os de uma simples constipação.

Recomendei então Panadol Gripus®, o qual consiste na combinação de 3 princípios ativos, nomeadamente 500 mg de paracetamol, 6,1mg Cloridrato de Fenilefrina e 100mg Guaifenesina. A escolha deste medicamento baseou-se no facto de ser eficaz no tratamento dos diversos sintomas da gripe sem necessitar de mais medicação auxiliar, uma vez que o paracetamol atua diminuído a febre, dores de cabeça e as dores corporais, o Cloridrato de Fenilefrina funciona como descongestionante nasal e a Guaifenesina que tem uma função expetorante no alívio da tosse. Indiquei que tomasse duas cápsulas a cada oito horas, conforme não excedendo seis cápsulas num período de vinte e quatro horas. Alertei que a duração do tratamento não deveria exceder três dias. No final do atendimento informei o utente que caso a febre não baixar ou aumentar nos próximos três dia deveria consultar um médico. [1]

7.2- Caso 2

Um senhor de 52 anos dirigiu-se a farmácia alegando não conseguir defecar a três dias, demonstrado estar bastante preocupado com esse problema e procurando uma solução rápida.

Em primeiro lugar acalmei o utente referindo que a obstipação não é uma doença, mas sim um sintoma relativamente comum na população, e que por isso não representa por si só uma patologia grave. De seguida perguntei se tem sentido alguma alteração no seu ritmo de vida, quer seja a nível laboral ou social, que o possa ter colocado numa situação de stress, ao

que me respondeu que se encontrava de férias mas que tinha nos últimos 5 dias estado a acompanhar um familiar próximo, o qual se encontrava hospitalizado devido a um acidente rodoviário. Perguntei então se durante esse período alterou algum hábito alimentar ao que me respondeu que não tinha perdido apetite, mas devido ao facto de permanecer no hospital com o familiar apenas tinha consumido "fast-food" nos últimos dias. Passei então a explicar que a razão por trás da obstipação se deveria ao facto de estar a vivenciar uma situação stressante, o que associado por ter uma alimentação carente de fibras desencadeou um atraso no transito intestinal.

Neste caso em primeiro lugar recomendei, como medidas não farmacológicas, que inicia-se uma dieta com um elevado aporte de fibras, nomeadamente a base de cereais integrais, leguminosas, frutos e legumes frescos, uma vez que as fibras vegetais não são digeridas e absorvem água, o que confere volume e plasticidade às fezes, acelerando assim o trânsito intestinal. Recomendei também a ingestão de mais líquidos, o que facilita o transito intestinal, e pratica de exercício físico, uma vez que esta para além de ajudar ao normal funcionamento do intestino reduz também os níveis de stress.

Como medidas farmacológicas, dada a urgência do senhor em resolver o problema recomendei a utilização de um laxante por contacto, dado serem a primeira escolha recomendada para o tratamento da obstipação ocasional, uma vez que apresentam um resultado mais rápido. Recomendei então a utilização de Dulcolax® 5mg em comprimidos revestidos, o qual é um laxante por contacto do grupo difenilmetano, o qual estimula a mucosa do intestino grosso provocando peristaltismo do cólon. Esta estimulação resulta numa evacuação mais rápida, com redução do tempo de trânsito intestinal e amolecimento das fezes. Recomendei que ingerisse dois comprimidos a noite, para que o movimento intestinal se produza de manhã. No entanto avisei o utente para não prologar o tratamento com Dulcolax® por mais de 3 dias, dado que não deve ser utilizado diariamente, uma vez que a utilização prolongada e excessiva poderá provocar desequilíbrio eletrolítico e hipocaliemia. Finalmente alertei que caso não se sentisse melhor ou se a situação piorar após 5 dias, deve consultar um médico. [2]

8- Conclusão

A realização deste estágio significou para mim o culminar de cinco anos de estudo trabalho e dedicação, permitindo-me exercer na prática as funções de um farmacêutico. Foi extremamente desafiante dada a minha falta de experiência, o que resultou muitas vezes em receios e incertezas da minha parte perante certas situações. No entanto o apoio,

acompanhamento e dedicação da equipa técnica no desenvolver das minhas capacidades foi imprescindível, incutindo-me responsabilidade, profissionalismo e espírito de equipa.

Foi também graças a este contacto com os utentes que me apercebi da extrema importância do papel do farmacêutico enquanto profissional de saúde, uma vez que somos a máxima autoridade no que diz respeito ao medicamento e muitas vezes somos o primeiro contacto que o utente procura para resolver os seus problemas de saúde. Devo também salientar o gratificante que é a confiança depositada pelos utentes em nós, a qual tentei retribuir através do melhor atendimento possível, demonstrando sempre total interesse e preocupação nas diversas situações que me surgiram. Sem dúvida este estágio reforçou imenso a confiança nos meus conhecimentos e permitiu-me estabelecer uma relação de proximidade bastante grande com a população, fazendo-me sentir o maior orgulho em contribuir para o bem-estar e satisfação dos utentes.

Apesar de ter passado momentos mais complicados onde senti dificuldades, quero agradecer a todos os membros da equipa técnica da Farmácia Gonçalves por todos os valores que me incutiram, pelo apoio incondicional, pela imensa paciência e compreensão que tiveram comigo e acima de tudo por todo o carinho que me deram ao longo destes seis meses de estágio. A todos eles o meu mais sincero obrigado.

9- Bibliografia

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