

REVIEW

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# The role of diosgenin in crohn's disease

Sunday Ogundepo<sup>1</sup>, Adinnu M. Chiamaka<sup>2</sup>, Mercy Olatinwo<sup>1</sup>, David Adepoju<sup>1</sup>, Matthias Taiwo Aladesanmi<sup>3</sup>, Ugwu Obiora Celestine<sup>4</sup>, Kingsley Chijioko Ali<sup>5</sup>, Ogochukwu Jennifer Umezina<sup>6</sup>, Janet Olasore<sup>1</sup> and Abdullahi Alausa<sup>1\*</sup>

## Abstract

Inflammatory bowel disease (IBD) is a chronic idiopathic inflammation that can grossly affect the entire gastrointestinal tract (GIT) from the mouth to the anus. Crohn's disease is the most known type of IBD and has been the focus of attention due to its increase in prevalence worldwide. Although the etiology is yet to be elucidated, recent studies have pointed out Crohn's disease to arise from a complex interaction between environmental influences, genetic predisposition, and altered gut microbiota, resulting in dysregulated adaptive and innate responses. The presenting hallmarks of Crohn's disease may include weight loss, nausea, vomiting, abdominal pain, diarrhea, fever, or chills. Treatment is usually done with many approved immunosuppressive drugs and surgery. However, a promising avenue from natural compounds is a safer therapy due to its safe natural active ingredients and the strong activity it shows in the treatment and management of diseases. Diosgenin, "a major biologically active natural steroidal sapogenin found in Chinese yam," has been widely reported as a therapeutic agent in the treatment of various classes of disorders such as hyperlipidemia, inflammation, diabetes, cancer, infection, and immunoregulation. In this review, an analysis of literature data on diosgenin employed as a therapeutic agent for the treatment of Crohn's disease is approached, to strengthen the scientific database and curtail the dreadful impact of Crohn's disease.

**Keywords:** Crohn's disease, Diosgenin, Inflammation, STAT3, NF- $\kappa$ B activity

## Introduction

Crohn's disease is an enervating and incorrigible persistent inflammatory bowel disease (IBD). Four years ago, over six million cases of IBD were reported globally with a reported increase in age prevalence rate from 79.5–84.3% per a hundred thousand population [1]. High Socio-demographic Index (SDI) locations revealed the highest amount of age-standardized prevalence rate ranging from USA (most prevalent) to Singapore (least prevalent). It is portrayed by mucosal inflammatory ulceration, which could grow along the gastrointestinal tract (GIT) yet most normally influence the distal small digestive system. IBD is characterized by inflammation of the transmural, affecting the thickness of the

entail wall [2]. While the pathogenesis of Crohn's disease (CD) is somewhat complex, it is imperative to note that the site of disease onset is activated by natural factors which derange the mucosal barriers, thus modulating the healthy stasis of the gut microbiota.

These principal factors (immune response, microbiota, and genetics) are affected by the individual's exposure which relates to other risk factors leading to Crohn's disease [3]. Modern treatment in Crohn's disease includes the use of immunomodulators (thiopurines and methotrexate), anti-inflammatory agents (corticosteroids), anti-tumor necrosis factor agents (anti-TNF), antibiotics, as well as surgical processes [4, 5]. A study showed that the usage of anti-TNF agents and thiopurines gave synergistic result that were effective in the management of Crohn's disease by about 50% [6]. However, Chinese yam (*Dioscorea opposita*), a regional crop in China [7] is of nourishing and fiscal importance. It is grown in the northeastern, central, and southeastern areas in China

\*Correspondence: [alausaopeyemi0@gmail.com](mailto:alausaopeyemi0@gmail.com)

<sup>1</sup> Department of Biochemistry, Faculty of Basic Medical Sciences, Ladoko Akintola University of Technology, Ogbomoso, Oyo State, Nigeria  
Full list of author information is available at the end of the article

having Henan province as the major growing region of *Dioscorea* species with the highest grade. The nutrients present in Chinese yam includes proteins with (3.59% - 8.93%), starches (43.7%), amino acids (2.31% to 7.26%), sugars (3.39%), vitamins and amylases [8–10]. While diosgenin is inarguably the most potent phytochemical in *Dioscorea spp* [11, 12], allantoin which is known to assist in wound healing, and speed up cell regeneration is also present in bountiful quantities in *Dioscorea spp* [13]. However, a steroidal saponin, particularly diosgenin is the exemplary phytochemical in *Dioscoreaceae* [11, 12].

Diosgenin denotes a C27 spiroketal steroidal saponin richly accessible in nature. Saponin, an active compound in plants like *Trigonella*, *Costus*, and *Smilax species* is found in *Dioscorea opposita* [14–16]. This steroid represents a great significance to industries and has been a subject important to numerous scientists worldwide throughout the years. Moreover, the therapeutically helpful steroidal medications, such as corticosteroids and sex hormones are derived in a semisynthetic manner from its active precursor diosgenin [17, 18]. Recently, studies reported that diosgenin possesses numerous biological activities such as hypolipidemic, anti-inflammatory, anti-proliferative, hypoglycemic activity, as well as a potent antioxidant [19–21]. However, further research have shown that diosgenin exhibits an immunosuppressive effect in inflammatory bowel disease via inhibition of NF- $\kappa$ B activity [22–26]. Taking into account that Crohn's disease is a chronic relapsing inflammatory disease, this review is aimed at illustrating the complex role of NF- $\kappa$ B activity and suggesting the active constituents present in Chinese yam (diosgenin) as a therapeutic agent for the management of Crohn's disease. This review further detailed the pathogenesis of Crohn's disease and as well explain the pharmacological role of diosgenin in the management of this disease.

### Pathogenesis of CROHN'S disease

Over the years, the outbreak of Crohn's disease has been recorded in several continents, particularly in Northern and Western Europe, also in North America regions [27]; 0.21% per year in North America, 0.16% per year in the United Kingdom and 0.09% per year in Northern Europe [28–33]. Minor cases are reported in Africa, South America, and Asia [27]. Study reports from epidemiologists revealed that women are even more susceptible to Crohn's disease than men and it is more common among individuals of Ashkenazi Jews [27].

Crohn's disease is associated with an imbalance in any part of the GIT contrary to ulcerative colitis, affecting the colon alone. However, the manifestation of this disease exhibited some certain diseases such as; ileocaecal disease (40%), ileal disease (30%), or colonic disease (25%).

There is the presence of anorectal abscess virtually in 30% of patients with this disease. Anatomical studies denoted Crohn's disease to be sporadic, leading to damages in the intestine ("skip" lesions), and the bowel infected with edematous and the accumulation of fat deposit on the serosal surface. Finally, there is the formation of Ulcer in the mucous membrane altering dispersed aphthous ulcers to profound serpiginous pleomorphic ulcers. These can delve into the intestines, resulting in the formation of a fistula between the infected intestines with the contiguous intestines, bladder, vagina, or skin [34].

Although the etiology of Crohn's disease is yet to be elucidated, recent studies from researches have proposed several mechanisms which suggest CD may result from genetic susceptibility, environmental factors, and intestinal microflora, leading to an aberrant immune response with a pact epithelial barrier function [35].

### Genetics

Genetic studies on twins and families attested an active genetic impact on the procurement of CD. For instance, it was confirmed in about 50 % of monozygotic twins together with 30 % of offspring of parents affected with CD [36]. The successful genome-wide association (GWA) studies with linkage analysis and positional cloning program have analyzed over 30 specific genetic loci that brought major insight to CD etiology. Some of the most strongly related gene susceptible to the role CD pathogenesis includes (CARD15/NOD2, IRGM, IL23R, LRRK2, and ATG16L1), interleukin 23 (IL-23) and T helper 17 (Th17), cell pathway (IL23R, IL12B (encoding IL-12p40), STAT3, JAK2, and TYK2) [37, 38].

The first gene discovered, Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) locus on chromosome 16q12 [39–41], is a cytosolic recognition receptor modulating the immune system against intracellular bacteria. However, 40% of western patients affected with CD exhibited three variations ((amino-acid substitutions Arg702Trp, Gly908Arg, and the frameshift FS1007insC) in the gene located within the leucine-rich repeat domain subjected for sensing muramyl dipeptide (MDP), a peptidoglycan component of both gram-positive and gram-negative bacteria cell wall [42]. NOD2 is expressed in diverse roles relating to several cellular processes including regulating panteth cell function, viral sensing, altering apoptosis in regulating T cell, and regulating autophagy [41]. Studies have revealed that defects in NOD2 expression affect the sensing of muramyl dipeptide which activates series of innate immune responses and bacteria-killing, leading to the tenacity of intracellular bacteria with an effect on antimicrobial role in the lumen [43–45]. In continuation, MDP activation resulted in regulating effects of inherent immune

system such as suppressing cytokine effects (IL-23 driven Th17 responses), repression of other protein recognition receptor (TLR-2 and TLR-4 responses) and initiation of tolerance (via IL-10 and decreased TGF- $\beta$ ) [46, 47]. In addition, the activation of MDP via NOD2, induces the recruitment of the Ser/Thr/Tyr kinase RIPK2, which is a significant approach to downstream signaling pathways activation which stimulate the activation of NF- $\kappa$ B signaling pathways and MAPK, modulating the production of effector molecules such as IL-8 [48–51]. IL-8, also known as neutrophil chemo-attractant denoting a pleiotropic proinflammatory cytokine developed from different stressors [52], also can be distinguished as an effective angiogenic factor relating to tumor growth and metastatic tumor [53, 54] and as biomarkers for many chronic inflammatory diseases [55–57]. As regards NOD2, it was revealed that several cellular components secretes IL-8 in response to the activation of NOD2 [58], with many groups which depict a decrease in IL-8 secretion in cells of CD patients due to NOD2 polymorphism [59, 60]. Furthermore, on the gene susceptible to the role of CD, the detection in polymorphism of autophagy gene (ATG16L1, LRRK2, and IRGM) from GWAs in CD has activated important research work in IBD. Autophagy has been studied to play a crucial role in organism on cellular survival, differentiation, development and homeostasis against various pathologies such as infections, cancer, neurodegeneration and aging [61]. Studies on ATG16L1 genes gave clear discernment on pathogenic results. However, two recent studies have revealed the defective autophagy response towards bacteria in the induction of CD. Cooney et al., (2010) revealed autophagy relations with NOD2; In reaction to MDP, autophagy is induced via receptor-interacting serine/threonine –protein kinase 2 (RIPK2), ATG7, ATG5 and ATG16L1 in dendritic cells. This reaction triggered the handling of bacteria through direct engulfment and successive propagation of major histocompatibility complex (MHC) class II for antigen-specific CD4+ T-cells responses in DCs [45]. Travassos et al., (2010) have also showed NOD2 to raise ATG16L1 to the plasmalemma at the entry point of bacteria to trigger xenophagy [62].

#### **Environmental factors**

Among the environmental factors hypothesized in CD, cigarette smoking has been found to be the most prominent epidemiology evidence in the pathogenesis of CD. It was revealed that smokers are likely to develop CD with a two-times increase compare to non-smokers [18–20] [63]. A study has revealed that the effect of cigarette smoking can cause severe damages to both innate and adaptive immune responses, causing increase to microbial infection which would aid its role in the etiology of

CD [64]. Over the past decade, the role of environmental and genetic factors has been the major research contributed to the etiology of CD. Also, it has been proven that extract from cigarette smoke could cause a setback in NOD2 mRNA expression leading to the deterioration of NOD2 activity in intestinal epithelial cells [65].

In addition, the impact of diet seems ambiguous in developing CD. However, certain studies have illustrated diet containing excessive number of sugars, omega-6 fatty acids, polyunsaturated fatty acids, total fat and meat increases the risk of developing CD but a diet rich in fiber and fruits lessened the growth of CD [66–68]. Also, the usage of non-steroidal anti-inflammatory drugs, aspirin, antibiotics, oral contraceptives and antibiotics are all connected with increasing the risk of CD [69–73].

Finally, the effect of epithelial differentiation and gut-related lymphoid tissue assembly in innate intestinal microbiota have been hypothesized to be involved in the pathogenesis of CD [74], changes in the disintegration of intestinal mucosa or modification in the gut microbiome appears to activate the growth of CD in the bowel [75]. The interface between the gut microbes and host T-cells is an epithelial layer. The secretion of host protective factors like defensins, and the surface mucus layer, as well as the autonomic nervous system and the basement membrane and the integrity of the epithelial cell influences the epithelial permeability. However, certain bacterial strains gravitate the change in bowel permeability in animal models, this alteration triggers an abnormal immune response showing increase in epithelial permeability in CD patients [76]. Patient affected with CD frequently show dysbiosis which includes increase in Gramma proteobacteria and Actinobacteria as well as decrease in Bacteriodes and Firmicutes bacteria [77].

#### **Immunological factors**

CD4<sup>+</sup> / T-helper cells, a key regulator in the immune system can be classified as Th1, Th17, Foxp3<sup>+</sup> regulatory T(Treg) cells [78]. In some patients with CD, there is overproduction of cytokines such as interleukin 12(IL-12) and interferon  $\gamma$  (IFN- $\gamma$ ) from the mucosal dendritic cells and macrophages leading to Th1 differentiation and inflammation within the intestinal mucosa [79]. High level of activated STAT4 and T-bet, IL-12 (Th1-associated transcriptional factor) was present in a nuclear extract from T-cells confined from inflamed Crohn's disease lesions [80]. Also, an embellished production of IL-18, a cytokine involved in perpetuating Th1 cells responses was revealed in the mucosa of patient with CD [81, 82]. Furthermore, in the membrane of patients with CD, there is abundant secretion of IFN- $\gamma$  lamina propria lymphocytes which appears to escalate a classic Th1 response resembling an acute infection process [83].

Several studies have been demonstrated on the role of Th17 cells in animals relating to gut inflammation and autoimmunity, of which there are few studies being examined on the effect of Th17 cells in patient with CD. A recent study in the lamina propria of patients with CD depicted an increased number of T-cells expressing retinoid-related orphan receptor- $\gamma$  (ROR $\gamma$ ), the great transcriptional factor for Th17 cells [84]. Pene et al. in their study isolated Th17 cells from deteriorated lesions of patient with Crohn's disease [85]. Furthermore, in both human peripheral blood and the gut from healthy individual as well as patients with CD, two autonomic studies were proved on Th17 cells [86, 87]. The Th17 designated cytokines (IL-17A, IL-17F, IL-22, and IL-26) are increased in the bowel and serum of patient with IBD, and Th17 cells having a stimulated phenotype shown in the intestinal mucosa and blood of patients affected with CD [88–91]. Moreover, the two studies depicted these cells in the expression of ROR- $\gamma$ +, IL-23R and CCR6, lacking CXCR3, a chemokine receptor designated for Th1 cells [86, 87]. Annunziato et al. in their study indicated IL-17A-producing T-cells in the intestine, with T-cells populations showing the expression of both IL-17A and IFN- $\gamma$ , denoted as “Th17/Th1” cells [86]. Acosta-Rodriguez et al. also determined Th17 cells to give the expression of CCR6 + CCR4+, as well as CCR6 + CXCR3+ expressing Th1 cells to produce both IL-17A and IFN- $\gamma$  [87].

Treg cells, which are expressed by Forkhead box P3 (FOXP3) are stable descent of dedicated regulator cells which play role in suppressing immune responses and perpetuation of relative constant condition within organism through resistance to self-antigens [92]. The operation of CD4+, CD25+ and sparse expression of CD127(IL-7 receptor) have been denoted to be the typical features of Tregs. In addition, the intolerance between the activated Treg cells as well as activated CD4+ T-cells is an expression of FOXP3, indicated as an explicit molecular marker [93]. FOXP3 regulatory roles are delineated in cell-cell interaction and the production of cytokines such as IL-10, IL-35 and TGF- $\beta$ . However, genetic variants of IL-10 and IL-35 with autoimmune disease conveys a recommendation in the etiology of IBD [94, 95]. Interestingly enough, studies on the impaired role of IL-10 receptor in human due to mutation have been delineated in a thorough clinical manifestation of CD [96]. Furthermore, studies have revealed that the upregulation of T-cells specific T-box transcription factor (T-bet), STAT, and the nuclear factor - $\kappa$ B (Nf- $\kappa$ B) proved an essential role in the development of IBD lesions due to an impaired suppressive Treg cell [97] (Fig. 1).

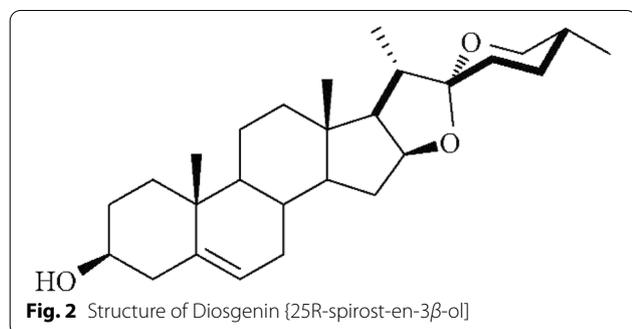
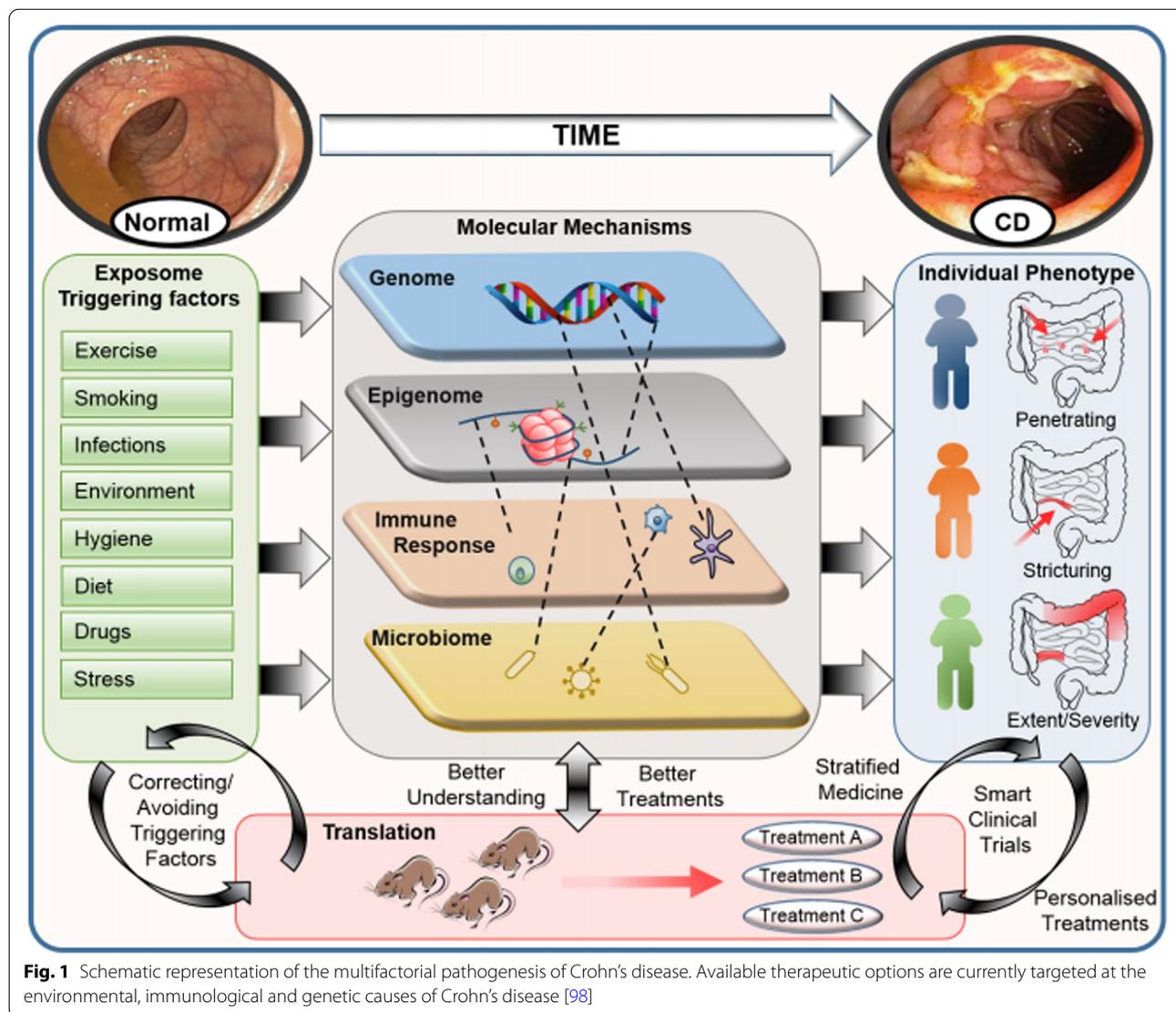
### Background of CHINESE yam

The genus *Dioscorea* includes more than 600 species of flowering plants in the *Dioscoreaceae* family, worldwide in tropical and temperate regions [13]. Chinese yam (*Dioscorea polystachya* and *Dioscorea opposita*), also known cinnamon-vine [99]. In the China language, it is referred to as *huáishān* [100], an endemic species of flowering plant with an important invigorant and economic relevance in China [7]. The northern, southern, and central region in China, commonly cultivates Chinese yam, and is widely distributed to some Asia countries such as Korea and Japan. General composition includes starches (43.7%), sugars (3.39%), proteins (3.59% to 8.93%), amino acids (2.31% to 7.26%), vitamins and amylases, amidst others [8–10]. Furthermore, various bioactive compounds are available in Chinese yam tubers such as diosgenin, choline [101], flavonoids and polyphenols [102], and allantoin, which shows a keratolytic effect, promoting cell regeneration and healing of wounds [11]. Decades ago, it was observed that dioscorin is a potential active agent with biological activities both in vitro and in vivo, encompassing the antihypertensive, epithelial cell protecting activities, immunomodulatory, lectin, antioxidant and enzymatic reactions [103]. A current literature backed the perception of extract from Chinese yam having the potential to inhibit Akt, MAPK, and Nf- $\kappa$ B signaling pathway [104].

Diosgenin, a major active constituent, occurs abundantly in *Dioscorea species*, *Heterosmilax species*, and *Trigonella foenum-graecum* [105]. It was confirmed that diosgenin has shown anti-diabetes effects [106, 107] anti-apoptosis [108] as well as mitigating oxidative stress [109–111] and inflammation [112]. Reports from pharmacological studies have revealed the anti-proliferative property of diosgenin, ameliorating the vascular system in a chronic renal failure model in rats by expanding the aorta eNOS expression in the rat [113] (Fig. 2).

### Role of DIOSGENIN in CROHN'S disease

The extract from Chinese yam, Diosgenin is a family of spirostanol steroid compounds having a C27 spiroketal steroids compound. It has a relative molecular mass of 414.62 and molecular formula to be C<sub>27</sub>H<sub>42</sub>O<sub>3</sub> [114]. Diosgenin is depicted as six rings, with the initials comprising of four rings, being the steroid core, together with the attachment of two latter rings in form of ketals. It is replaced with an OH group situated exactly at the 3 $\beta$  position of the first ring, with a double bond at the 5–6 position as well as a R-Configuration at position 25. One of its glycosides, dioscin is attached to the 3 $\beta$  position of diosgenin to form saponins, often seen to be a major bioactive saponin with the effects against hypolipidemia, inflammation, allergy, viral, fungal and



immunoregulation [115–117]. In addition, studies have revealed that diosgenin ameliorated cholesterol secretion via the biliary excretion, restrained cholesterol absorption [118–121], altered lipoxygenase activities caused by

differentiation of human erythroleukemia cell line [122], as well as cell cycle suspension in osteosarcoma cell line of human [123]. In the pathogenesis of inflammatory bowel disease (crohn's disease and ulcerative colitis), NF-κB has been identified to be one of the key regulators in the complex mechanisms such as; signaling mechanism via epithelial cells, dysregulated cytokine production, lymphocytes and macrophages. However, the transcription factor NF-κB is expressed and activated strongly in the inflamed bowel of patient affected with IBD. Studies carried on an inflamed gut from macrophages and epithelial cells of an IBD patient depicted an increased level of NF-κB p65 [124]. The increased level of NF-κB expression in macrophages led to the production and secretion of certain pro-inflammatory cytokines such as; TNF-α, IL-1, IL-6, IL-12 and IL-23 which are directly affected

in the mucosal tissue damage relating to IBD [125, 126]. Also, lamina propria fibroblast have been hypothesized to show a NF- $\kappa$ B pro-inflammatory role in IBD [127]. However, a proven study on the effect of diosgenin on a bacteria-recombinant human tumor necrosis factor (TNF- $\alpha$ ) showed that diosgenin inhibited TNF mediated NF- $\kappa$ B activation and its regulated genes products {c-Rel, RelA (p65), Rel B, NF- $\kappa$ B1 (p50 and p105) and NF- $\kappa$ B2 (p52)} in a dose dependent manner at 50  $\mu$ m and a complete annulling of NF- $\kappa$ B activity at 100  $\mu$ m [128]. Furthermore, the use of Western Blot analysis of an antibody detecting only serine phosphorylated form of I $\kappa$ B $\alpha$  affirmed that diosgenin completely suppressed TNF-induced I $\kappa$ B $\alpha$  phosphorylation (inhibitory subunit of NF- $\kappa$ B) in 5mins [129]. Thus, it has been proven that diosgenin inhibits the activation of NF- $\kappa$ B by inhibiting the degradation and phosphorylation of I $\kappa$ B $\alpha$ . Lastly, corticosteroids, a natural precursor of diosgenin [16, 17] has been approved to be an immunosuppressive drug on IBD, used to induce an over-expression of I $\kappa$ B $\alpha$  which is known to retain NF- $\kappa$ B in the cytoplasm together with the interaction of p65 to inhibit the activation of NF- $\kappa$ B [26, 130–134]. Over the years, the research community have implicated the role of inflammation and the impact of free radical induced oxidative stress in the pathogenesis of Crohn's disease, thus focusing therapeutic options toward the inhibition of inflammatory factors as well as scavenging free radicals [135–137]. The pharmacological potential of diosgenin is well placed beyond reasonable doubt. Quite a credible number of in vivo studies have shown the pharmacological potential of diosgenin to significantly ameliorates decreased body weight caused by a compromised immune system during the diseased state and elevated stool. This amelioration is however due to the suppression of inflammation by diosgenin [138–140]. The activity of oxidant such as superoxide radical, oxygen radical amidst others have been known to trigger the damage of tissues leading to the infiltration of neutrophils [141, 142]. This however leads to the secretion of myeloperoxidase which is transported within the cellular organelles to the suicide bag. The activation oof the neutrophils under duress are followed by the inflammation of the large intestine, which is however responsible for increased synthesis of reactive oxygen species [143]. As a result, the increased ROS synthesis following elevated MPO levels is responsible for inflammation attributed to Crohn's disease [144, 145]. A very recent study by Wang et al., (2018) [146] illustrated the anti-inflammatory potential of diosgenin. Over the years, studies have stressed the link between oxidative stress (caused by an imbalance between oxidants and antioxidant synthesized in the body and the pathogenesis of inflammatory bowel diseases including Crohn's [139, 140]. It was explained

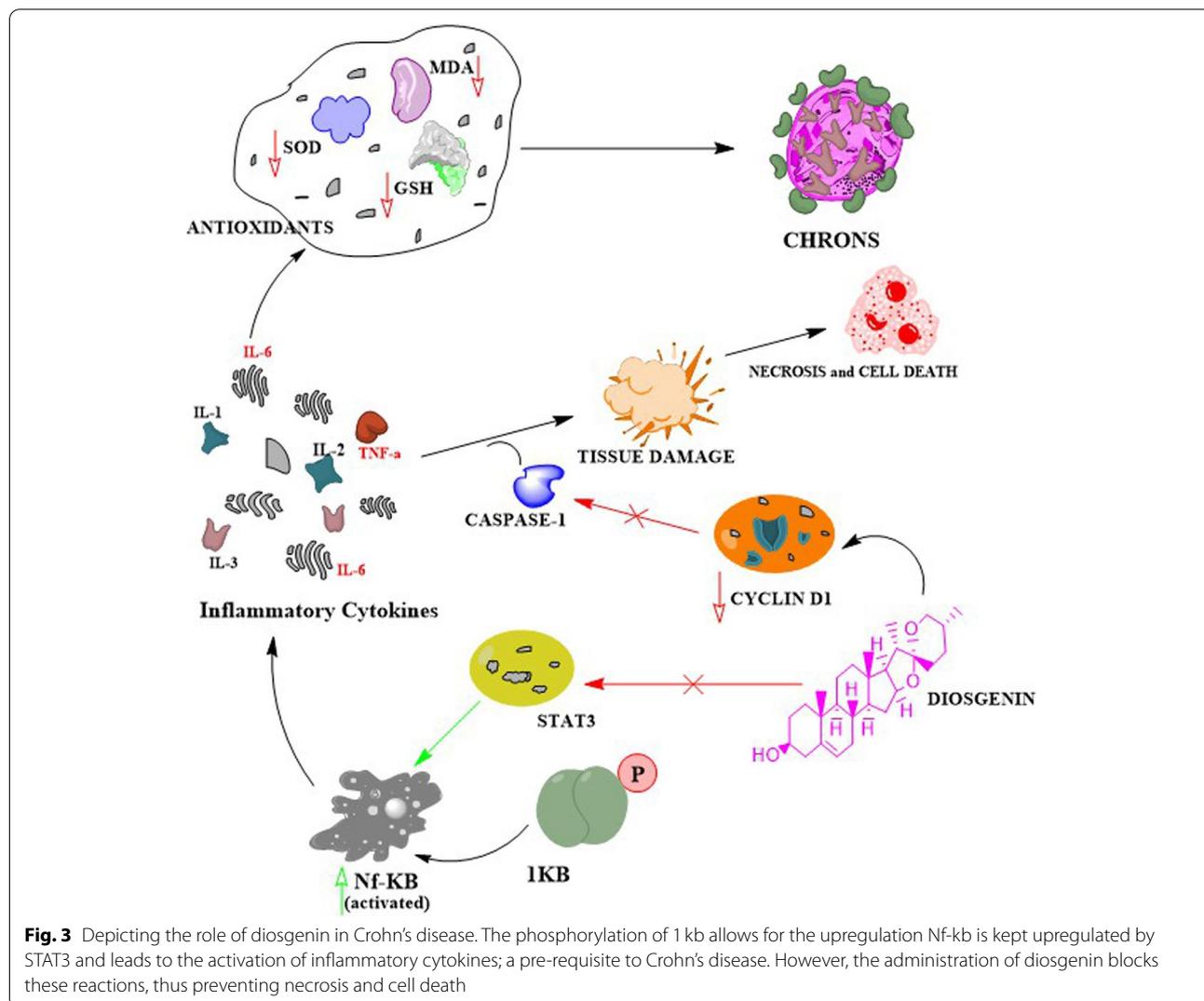
that the conversion of (O<sub>2</sub><sup>-</sup>) to hydrogen peroxide leads to the disruption of intestinal membrane, causing injury to cells. However, this reaction can be reversed by glutathione. Thus, sufficient glutathione levels are enough to avoid the onset of oxidative stress [147–149]. The reversal of lipid peroxidation by diosgenin is also worthy of notable mention [150, 151]. A correlation between the levels of multifunctional cytokines (inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IFN- $\gamma$ ) and the pathogenesis of Crohn's via the inhibition of regulatory T-cell function and activation of T helper type 1 (Th1) cells [139–152]. However, it was observed that administration of diosgenin lead to the attenuation of these inflammatory cytokines thereby expressing its essential anti-inflammatory potential in the management of Crohn's diseases [146, 153]. The intrinsic or extrinsic cell death cascade is triggered follow the onset of Crohn's diseases following the expression of Bax and Caspases-1 [154, 155]. However, investigation have reported the efficacy of diosgenin in inhibiting Bax and Caspases-1 induced apoptosis [156]. This was observed to be in accordance to the findings of Raju et al. (2004) on diosgenin [157]. Although the management of IBD with herbal mixtures is beginning to gain prominence, the effectiveness of diosgenin have however been placed beyond reasonable doubts in clinical research especially in the management of IBD. Several other pharmacological potentials of diosgenin have been include its anti-cancer effects, suppression of lipoxigenase inhibition of CXCR3, and induction of Ca<sup>2+</sup> release [158–160]. An essential factor in the regulation of genetic products are the signal transducer and activator of genetic products (STAT) family, playing important role in proliferation and survival of cells. This factor (STAT) becomes activated via the upregulation of by Janus kinases (JAK), or the Src family kinases, thus allowing STAT to dimerize and translocate while binding to the promoters of target genes [161, 162].

Of this large family, STAT3 is the most linked family associated with the promotion of the pro-inflammatory cytokines as well as supporting the growth of malignant cells. This is done by upregulating NF- $\kappa$ B, a deleterious factor whose effect have been discussed in this section. Briefly, the NF- $\kappa$ B-regulated Interleukin 6 (IL6) binds to IL6 receptor which via interaction with few subunits leads to the activation of (STAT)3. This in return regulates the activity of (SOCS) 3; essential in the suppression of cytokine activity [163, 164]. SOCS group of protein are involved in the negative feedback regulation of the JAK/Src family kinases, thus invariably regulating the signaling of STAT. The expression of SOCS3 have been found in IBD rat mode, thus suggesting a possible role in the pathogenesis of Crohn's and Colitis [165, 166]. The role of IL6/STAT3/SOCS3 in the regulation of homeostasis have

been well explained, as such the inflammation observed in Crohn's disease is as a result of the striking imbalance between SOCS3 expression and IL6/STAT3 signaling [167, 168]. It is worthy to note, IL6/STAT3 signaling, including constitutive activation of STAT3, was found to generally mediate development and progression of colorectal adenoma and carcinoma without inflammation in background [168, 169], in which IL6/STAT3 may be activated by microbial translocation through impaired mucosal barrier and function in physiological modulation of mucosal immunity (Fig. 3).

The pharmacological significance of diosgenin on STAT3 phosphorylation was observed to be in correlation with the repression of upstream c-Src, JAK1 and JAK2 protein kinases. Earlier investigation suggested that the role of Src and JAK1 kinase activities acts in synergy to regulate the constitutive activation of STAT3 [170, 171]. However, the findings by Feng et al., (2009)

[172] suggested that diosgenin blocks the synergistic cooperation of Src and JAKs involved in tyrosyl phosphorylation of STAT3. Furthermore, the mechanism at which JAK2, mitogen-activated protein kinase, and Akt activates STAT3 activation have been explained beforehand [173, 174]. Albeit, suppression of IL-6-induced Akt activation and nuclear translocation was pharmacologically mediated by diosgenin [172]. This however suggests that diosgenin exerts its pharmacological potential in quite diverse ways. While we have stated that diosgenin is capable of inactivating NF-kB, it was reported that STAT3 prolongs NF-kB retention via the acetylation of acetyltransferase p300-mediated RelA acetyltransferase p300-mediated RelA [175]. Some glittering evidences also showed that diosgenin-triggered inhibition of STAT3 activation is only possible via the recruitment of protein tyrosine phosphatase (PTP) [176, 177]. The biochemical significance of PTP can be properly read from studies by



Servidei et al., (1998) and Aggarwal et al., (2009) [178, 179]. While the stimulation of the expression of SH-PTP2 protein leading to the downregulation of constitutive STAT3 phosphorylation is clear, it is however safe to say that the diosgenin however possess a strong pharmacological basis that could be essential in the management of Crohn's disease.

### Conclusion & future perspective

The quest to provide therapeutic solutions to several medical conditions have been a cause of concern not only to the scientific community, but to human population at large. Scientists in the field of drug discovery and development works round the clock to ensure that the mayhem caused by this disease are put to check. Diosgenin is one of the major bioactive compounds found in Chinese yam. Several preclinical studies as regard its pharmacological activities against hypolipidemia, diabetes, cancer, inflammation, allergy, viral and fungal infection have been detailed. We observed that diosgenin inhibited TNF mediated NF- $\kappa$ B activation and its regulated genes products {c-Rel, RelA (p65), Rel B, NF- $\kappa$ B1 (p50 and p105) and NF- $\kappa$ B2 (p52)} in a dose dependent manner, thus it is potent in the management of Crohn's diseases. While invivo studies has affirmed the efficacy of diosgenin, the challenge to conform invivo studies to human clinical trials still persists. The shift of focus to genetic approach in developing a therapeutic agents should be applauded. Although limited amount of translational research still remains a problem to contend with in the scientific community, future studies should endeavor to shed more light on the use of emerging technologies as a powerful agent in the development of Crohn's diseases therapy.

### Abbreviations

IBD: Inflammatory bowel disease; CD: Crohn's disease; anti-TNF: Anti-tumor necrosis factor; NF- $\kappa$ B: Nuclear factor kappa light chain enhancer of activated B cells; GWA: Genomics Wide Association; NOD2: Nucleotide-binding oligomerization domain-containing protein 2; MAPK/ERK: Mitogen-activated protein kinase; IL-3: Interleukin-3; IL-12: Interleukin-12; JAK 3: Janus Kinase 3; MDP: Muramyl dipeptide; IRGM: Immunity related GTPase family M; IFN- $\gamma$ : Interferon-gamma; Th17: T helper 17; TLR-2: Toll-like receptor -2; ATG16L1: Autophagy-related 16-like 1; CARD 15: Caspase recruitment domain 15; IL23R: Interleukin 23- receptor; LRRK2: Leucine-rich repeat kinase 2; TGF- $\beta$ : Transforming growth factor- $\beta$ ; RIPK2: Receptor-interacting protein serine-threonine kinase 2; IKBa: Inhibitor of kinase B- $\alpha$ ; CCR6: Chemokine receptor 6; Foxp3: Forkhead box P3; STAT3: Signal transducer and activator of transcription 3; TYK2: Tyrosine kinase 2; ATG7/5: Autophagosome 7/5; MHC: Major histocompatibility complex; CXCR3: Chemokine receptor 3.

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### Authors' contributions

Author AA conceived the idea; Author OS, OM, OJ, AD and OJ gathered information and developed the manuscript; Author AA proofread and edited

the manuscript. All authors read and approved the final manuscript for submission.

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#### Ethics approval and consent to participate

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#### Consent for publication

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#### Competing interests

Authors declare that they have no competing interest.

### Author details

<sup>1</sup>Department of Biochemistry, Faculty of Basic Medical Sciences, Ladoko Akintola University of Technology, Ogbomoso, Oyo State, Nigeria. <sup>2</sup>Department of Food Science and Technology, Micheal Okpara University of Agriculture, Umudike, Nigeria. <sup>3</sup>Department of Human Nutrition and Dietetics, Faculty of Public Health, University of Ibadan, Ibadan, Nigeria. <sup>4</sup>Department of Pharmacology, Faculty of Pharmaceutical Sciences, Enugu State University of Technology, Enugu, Nigeria. <sup>5</sup>Department of Biochemistry, Faculty of Biological Sciences, University of Nigeria, Nsukka, Nigeria. <sup>6</sup>Pharmacology/Physiology Unit, Department of Science Laboratory Technology, University of Nigeria, Nsukka, Nigeria.

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