Susceptible genetic polymorphisms and their association with adverse effects of orlistat therapy

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Graphical Abstract

Abstract

Orlistat is a tetrahydrolipstatin, which inhibits both pancreatic and gastric lipase enzymes in the gut and prevents the absorption of dietary fats in the intestine. Therefore, it is widely used as an anti-obesity medication to control and manage body weight in obese patients worldwide. Despite this, the mounting number of clinical studies report that orlistat treatment induces adverse effects like pancreatitis, hepatic failure, kidney stone, acute oxalate nephropathy, and others. Although various factors could mediate the adverse effects of orlistat, emerging shreds of evidence suggest that genetic polymorphism-associated factors could be the primary reason for the cause. Hence, in this review, we first collated the most critical clinical adverse effects caused by orlistat and then appraised the susceptible genetic polymorphism that could further worsen the adverse effects of orlistat. Nonetheless, this review warrants similar conceptual approaches to understand orlistat's adverse effects in the selective genetic polymorphism and improve the therapeutic outcome of orlistat.

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1. Introduction

Orlistat is one of the widely used drugs, approved by the Food and Drug Association (FDA) as well as the European Medicines Agency (EMA) for the treatment and management of obesity (Kang and Park, 2012). It is a carboxylic ester, tetrahydrolipstatin (THL) which inhibits the lipase enzymes responsible for triglyceride hydrolysis by binding covalently with the active serine site in gastric and pancreatic lipases enzymes. Several interventional studies report the possible associations of orlistat intake with the progressive adverse outcomes. The adverse consequences of orlistat therapy include gastrointestinal dysfunction, pancreatitis, sub-acute hepatic injury, acute oxalate nephropathy, and renal failure (Davidson et al., 1999; Finer et al., 2000; Kose et al., 2015; Qi, 2018). Therefore, it is necessary to understand the underlying factors by which the adverse effects of orlistat could be avoided or minimized.

It is well regarded that lifestyle factor is not the sole reason for acquiring obesity. It also depends on the genetic factors and the intrinsic interactions between the environment and genetic factors. Therefore, the current research interests are progressing on the potential implications of

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pharmacogenomic basis to improve the therapeutic outcomes of anti-obesity medicines. Several clinical studies have reported the adverse drug reactions (ADR) of orlistat, but genetic factors in the pathogenesis of orlistat-mediated adverse effects are less studied.

Among the various genetic polymorphisms associated with obesity, the perilipin, *PLIN* 11482 G>A (rs894160) locus gene has been reported to be pivotal in weight reduction (Corella et al., 2005). The other obesity-related genetic polymorphisms includes *AGRP*-38 C>T (rs5030980), *MC4R* T>C (rs17782313), *POMC* C>T (rs1042571), *APM1* G>T (rs2241766), *ADRB2* C>G (rs1042714), *APOA2*-492 T>C (rs3813627) etc., (Basiri et al., 2015; Rana et al., 2018; Srivastava et al., 2016; Wu et al., 2014). Though a few genetic polymorphisms have been reported for obesity, only very few studies have been carried out to co-relate the genetic influence on orlistat therapy. For instance, a recent randomized control clinical trial conducted in South Korea in 2019 for the first time demonstrated the *CYP2B6*6* allele influence on orlistat and the associated change in patient pulse rate, suggesting the significance of pharmacogenomic factors influencing therapeutic outcomes of orlistat (Hwang et al., 2014).

The following contents collate the reported adverse effects of orlistat and the susceptible genes associated with orlistat-mediated adverse effects and their possible intrinsic associations.

2. Reported disease-associated mechanism and clinical adverse effects of orlistat

Mounting clinical studies show that orlistat generates undesirable adverse effects in patients with obesity. These adverse effects include pancreatitis, sub-acute hepatic failure, steatorrhea, diarrhea, abdominal pain, cholelithiasis, non-alcoholic fatty liver diseases, etc (Davidson et al., 1999; Finer et al., 2000). Selective studies reported that orlistat therapy led to adverse effects including, depression, headache, hypertension, and lassitude in the nervous system (Ferraz et al., 2004; Hwang et al., 2014). Likewise, in some cases, blocking fat absorption by orlistat also leads to acute oxalate nephropathy, constipation, polyuria, polydipsia, and lower-leg edema in the renal functions Table 1(Nwobodo et al., 2015; Zohrabian et al., 2010).

Table 1- The list of reported adverse effects with orlistat therapy

System	Adverse effects	References
Gastrointestinal system	Fatty and oily stool, faecal urgency, diarrhea, flatulence, intestinal discomfort, irritable bowel syndrome (IBS), bleeding, gallstones, pancreatitis, acute cholestatic hepatitis, acute hepatic failure, and severe liver damage.	Davidson et al., 1999; Finer et al., 2000
Nervous system	Depression, headache, forgetfulness, malaise and lassitude	Davidson et al., 1999; Finer et al., 2000; Thorleifsson et al., 2009
Renal function	Hyperoxaluria, acute kidney injury, acute oxalate nephropathy, kidney failure, constipation, polyuria, polydipsia.	Thorleifsson et al., 2009

2.1 Gastrointestinal disturbances

A meta-analysis reported that orlistat dosage of 120 mg three times a day in obese patients showed modest elevation in GI disturbances compared to placebo (Jain et al., 2011). Orlistat-induced GI adverse effects are a significant concern, and they were mostly related to high feces fat, steatorrhea.

2.2 Acute pancreatitis

Acute pancreatitis (AP) is mainly confirmed with the initiation of the parenchyma cells and peri-pancreatic fat cell injury that is linked towards inflammation in individuals. The AP is primarily identified in patients having mild and/or severe pain in the abdomen. The inception of parenchymal and peri-pancreatic fat necrosis with allied inflammation will lead to AP. It is characterized by

acute intense pain in the stomach and severity (Whitcomb et al., 2013). Elkhouly and his authors reported that the class-III drugs, including orlistat, could cause AP (Elkhouly et al., 2019). A recent study by Kose et al. reported that a 54 years old man who started treatment for obesity with orlistat had reported severe abdominal pain within a week. Upon further investigation with tomography, the patient has diagnosed with peripancreatic fat edema, one of the symptoms of AP. Although the study was inconclusive on how orlistat induces AP, it warranted further investigations (Kose et al., 2015). Likewise, few clinical studies reports that orlistat therapy was associated with the progression of AP (Chaudhuri et al., 2013).

2.3 **Sub-acute hepatic failure**

Acute liver failure (ALF) is a complex multi-factor disorder that progresses on liver damage and leads to blood and brain disorder in a minimum interval of time. The etiology of severe ALF remains underdetermined. Morris *et al.* have shown that orlistat has also inhibited carboxylesterase in the liver, the enzyme primarily responsible for detoxification and liver protection. (Morris et al., 2012). A 35-year-old woman who was moderately obese with sub-acute hepatic failure undergone liver transplantation was treated with orlistat 120 mg/day (Umemura et al., 2006). After three weeks, a usual laboratory check demonstrated severely impaired liver function. In the same way, multiple hepatic failure cases were reported among different age groups and from diverse global populations. This evidence further justified orlistat with sub-acute hepatic failure (Asplin et al., 2002; Persson et al., 2000).

Among 94,695 patients administered orlistat, about 988 patients were identified with liver injury in which 335 cases were definite, and 653 cases were identified as probable cases (Douglas et al., 2013). The increase in the occurrence of liver injury has been detected in the time of 90 days after the orlistat treatment, and the occurrence ratio is 1.50 (95% confidence interval 1.10 to 2.06). The liver injury occurrence has been doubled after the orlistat treatment (30 days). Hence, the report proposing that the therapy with orlistat accord with the elevated risk of liver injury (Douglas et al., 2013).

2.4 Acute oxalate nephropathy

The incidence of nephrotoxicity was said to be associated with the orlistat intake. Intake of orlistat in a Caucasian woman has been reported to cause acute kidney injury (AKI) called acute oxalate nephropathy. The unabsorbed dietary fat and bile acids react with calcium and inhibit their binding to the oxalates, resulting in hyperoxaluria, an increased intestinal oxalate absorption (Ferraz et al., 2004). The study report shows that the biopsy of the kidney has an accumulation of calcium oxalate crystals (COC) within the tubular lumen, suggesting the orlistat intake has potential risk for kidney stone formation in patients

3. Reported adverse effect associated with genetic polymorphism:

3.1 Genetic polymorphism of Gastrointestinal disturbances

Gene polymorphisms are considered one of the significant factors involved in developing functional gastrointestinal disorders (FGID). In a study, 79% of orlistat consumers reported at least one gastrointestinal adverse event (Heck et al., 2000). Since orlistat acts in the GI system by stimulating faster gastric emptying and altering the incretin response to a high-fat meal, there are chances for GI-associated susceptible polymorphisms to aggravate or alleviate GI effects of the drug (Filippatos et al., 2018). For example, patients with *TNFSF15* gene polymorphism are susceptible to IBD (Zhu et al., 2019).

Saito *et al.,* carried out a pilot study trial with 49 IBS patients with mild to severe GI pain and showed a reduction in Na^+ ions in patients, whereas this was not observed in healthy volunteers (Saito et al., 2010). Hence providing orlistat therapy to the population with *SCN5A* and *TNFSF15* gene polymorphisms may result in a higher chance of GI side effects than in a typical wild-type population.

3.2 Genetic polymorphism of acute pancreatitis

Orlistat inhibits pancreatic and gastric lipases to exhibit its action, and this could trigger acute pancreatitis and thus obese patients are cautioned at risk of pancreatitis (Ahmad and Mahmud et al., 2010). Patient's with pancreatic disorder susceptible gene such as *PRSS1-PRSS2, SPINKI, CTRC, CTSB* may increase the chances of orlistat induced pancreatitis in orlistat therapy. Some of the genetic polymorphisms that may affect pancreatitis are specified below.

3.2.1 *PRSS1-PRSS2* Locus

The *PRSS1* is the significant component of cationic trypsinogen and is easily activated. The *PRSS1* gene is positioned on chromosome 7q34 and is said to improve the mutation function that helps to increase the activation of trypsinogen (Whitcomb, 2013). The noncoding regions of *PRSS1-PRSS2* locus are at the substitution at rs10273639 on A/T to C. The influence of the expression of *PRSS1* is found to be directly associated with AP (Whitcomb et al., 2013). Polonikov *et al.,* studied a Russian male population and reported that the C allele is the major gene linked with the AP in both alcohol and smoke-consuming patients (Németh and Sahin-Tóth, 2014; Polonikov et al., 2017). Studies conducted in surgical specimens of 592 Swedish colorectal cancer patients, trypsin helps the pancreatic cancer cells to invade and migrate by digesting the basement membranes and extracellular matrix (Williams et al., 2001; Yi et al., 2016). The unusual amount of trypsin is directly related to pancreatic cancer outcomes and decreases the survival rate in pancreatic cancer cases. The level of trypsin present in the serum is influenced by numerous factors that include changes in the *PRSS1*. Based on the earlier studies, it was evident that the expression of the trypsin is high in the pancreatic tissues with *PRSS1* mutation patients and was allied with the rs10273639 genotypes in newly born babies along with the sepsis. Findings suggest that the elevation in the promoter's transcriptional activity or enhancement in the unusual trypsin stability to elevate the trypsin quantity is due to the *PRSS1* genetic variations (Zhang et al., 2017).

3.2.2 *SPINK1*

The inhibition of trypsin by *SPINK1* is a defensive action to counter the stimulation of trypsinogen. Though we have unclear mechanistic action of *SPINK1* N34S towards pancreatitis, and it was believed that mutation reduces the capability to constrain trypsin (Koistinen et al, 2016). Analyses of 371 patients and 459 controls show that the high vulnerability of AP is due to *SPINK1* N34S and two independent studies conducted in India and Poland (Koziel et al., 2015; Midha et al., 2010). However, this polymorphism was familiar in the general population with an approximate frequency of 2% (Räsänen et al., 2016).

3.2.3 *CTRC*

The twin paradoxical pathways by *CTRC* have been implicated in trypsinogen's auto-activation. The findings from a study conducted on 584 Indian chronic pancreatitis patients had indicated that the increase in the risk of pancreatitis was due to the polymorphic, synonymous variant of *CTRC*-180 C > T gene polymorphism (Paliwal et al., 2013). One of the recent papers reported that the occurrence of the AP is possibly mediated by mutation (Koziel et al., 2017, Mahurkar et al., 2006), which comprises post-transcriptional processing in which synonymous alternant that shows its impacts on the manifestation of AP. The predisposition in an intensive ailment in controlled numerals of patients and the polymorphism and *SPINK1* N34S may specify the significant action of the genetic alternant in AP. The exacerbation of the illness is due to those multi-gene elements (Weiss et al., 2007).

3.2.4 CTSB

Selective studies reported that polymorphism in *CTSB* 595 *C > T* gene would lead to chronic pancreatitis due to irregular localization/ premature triggering of trypsinogen. This human gene is around 25.6 kb. Further extensive studies on *CTSB* gene polymorphisms took part in multiple populations, including Indian and European people; those studies revealed identifying the direct association of Val26Val polymorphism, Ser53Gly at single-nucleotide polymorphisms (SNPs) in patients and controls respectively in case of tropic calcific pancreatitis. Later it was understood that the polymorphism *L26V* was highly significant in both *N34S* (positive and wild type) patients denoting that *CTSB* is independently associated with disease condition. Numerous research studies established that *CTSB* 595 *C > T* polymorphisms are closely associated with pancreatitis. It is noteworthy that a significant variation was observed in *CTSB* in the patients with pancreatitis even without any mutations in the *PRSS1* gene and N34S *SPINK1,* suggesting that *CTSB* could progress pancreatitis independently. But, the *CTSB* was not reported in European patients with idiopathic chronic pancreatitis (Powell et al., 2001; Smithies et al., 2000).

3.2.5 Genes that cause pancreatitis through inflammatory pathways
3.2.5.1 Interleukins

The interleukin families possess an active part in the evolution of AP. The pro-inflammatory mediators, interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α), are liberated and accelerates inflammatory chain reactions during the period of AP. Plentiful cytokines are

present in the interleukin family that is concerned in AP. The study conducted in 116 patients and 170 healthy volunteers in England showed that 3 of 5 polymorphisms in intron 2 *IL-1RN* gene encrypts the receptor antagonist IL-1 and helps govern AP intensity and the idiopathic AP (IAP) susceptibility (Yin et al., 2013). The variable data of these findings make it indistinct that this reported genetic polymorphism is an essential part of AP through governing the associated proteins or just a passerby in the evolution of AP (Rahman et al., 2004).

3.2.5.2 Antioxidant Enzyme Genes

Oxidative stress is a pivotal intermediary in AP, which plays a paradoxical role. The stimulation in the generation of reactive oxygen species (ROS) occurs by injured acinar cells, which consequential in less intense ailment evolution by generating apoptosis. Fascinatingly, in experimental studies, the ROS inhibition proliferates the local and systemic inflammation through discharging the inflammatory mediators required to produce necrosis of acinar cells. The glutathione S-transferase (*GST*) family consists of genetic alternates that act as an anti-oxidant enzyme and are delineated to be comprised in AP. The GST catalyzes the binding of glutathione (GSH) to free radicals, chiefly comprises of 4 subclasses (namely, A, M, P, and T) in pancreas (Martins et al., 2017). The GSH is a scavenger for ROS and exhaustion of GSH may go along in leading to AP. The *GST* genes comprise numerous polymorphisms that are allied with the incidence or sternness of AP as unlike clinicians. Caspase, the foremost originator of apoptosis and defends acinar cells contrary to necrosis. The study conducted on the Portuguese population, including 133 AP patients and 232 healthy controls, showed that the *CASP9* Ala28Val polymorphism (rs1052571), situated in an intron of caspase-9, reduces minor kind of AP (Sakai et al., 2003). The multifaceted mechanism involved in oxidative stress with pathogenic apoptosis in AP needs explication before a beleaguered orlistat therapy can be established.

3.2.5.3 Macrophage Migration Inhibitory Factor (MIF)

MIF shows a significant pro-inflammatory role in AP along with TNF-α and IL-1, specifically in extreme cases. Few studies show an increased level of serum MIF acts as an indicator for analyzing the intensity of pancreatic necrosis in AP (Makhija et al., 2007; Seo et al., 2007). In the UK, 164 AP patients' analyses exhibited that the *MIF*-173 (rs755622) polymorphism allied with AP compared with SAP and that the *MIF*-173C allele was suggestively amplified in AP cases. Further

researches are required to explicate the mechanistic action present in the activities of *MIF* gene polymorphisms on AP (Özhan et al., 2010; Chen et al., 2017).

3.2.5.4 PTGS2

Cyclooxygenase (COX) is a central component in the regulation of prostaglandin formation. Prostaglandin produces inflammation, endorse vasodilation, and upsurge capillary penetrability. Some of the previous studies provide data that COX-2, an isoform of COX, is allied in AP's progression and prevents COX-2 by specific non-steroidal anti-inflammatory drugs (NSAIDS); for example, indomethacin and diclofenac, may enrich the sternness in AP. Depending on the vibrant action of COX-2, Turkey clinicians worked on 7 *COX-2* SNPs in the resident populace. They discovered that the rs5275 polymorphism in the 3′-untranslated section of the *COX-2* gene was allied with vulnerability towards AP (Fang et al., 2015; James et al., 2015).

3.2.5.5 Genes regulating for Angiotensin-Converting Enzyme

The renin-angiotensin system (RAS) is vital in maintaining blood pressure. The angiotensin-converting enzyme (ACE) is directly associated with RAS for converting the angiotensin I to angiotensin II that acts as a vasoconstrictor. Therefore, the specific RAS in the pancreas directly correlates with AP, as the RAS activates the inflammatory signaling pathway by activating the immune cells to release proinflammatory cytokines, which is one of the causes leading to AP. Fang *et al.* carried a meta-analysis study on the polymorphism involved with the *ACE* gene in association with the risk of AP, and the study consists of 3 countries with 544 patients and reported that this polymorphism is directly associated with alcohol-related AP (Fang et al., 2015). The authors have also reported that there will be impairment in the mitochondria causing chronic hypoxia on continuous alcohol intake and thus leading to AP.

3.2.5.6 Myosin IXB (MYO9B)

The myosin molecule (MYO9B) encodes to participate in maintaining the functions of the gastrointestinal mucosal barrier by altering the position and assembly in the tight junction (Monsuur et al., 2005). Nijmeijer *et al.* carried out a cohort study using Dutch and German patients with AP, and they reported that the two polymorphisms in MYO9B were susceptible to AP, and also a non-synonymous variant rs1545620 A/C showed a closer correlation in Dutch patient shaving AP (rs7259292; rs1545620) (Nijmeijer et al., 2013).

3.3 Genetic polymorphism of Sub-acute hepatic failure

Even though the mechanism of acute hepatic failure in orlistat therapy is not well known, studies have been conducted to identify the effects of genetic polymorphisms associated with fatty liver in obesity and nonalcoholic fatty liver. The study reports suggested that gene polymorphisms such as *PNPLA3*, *TNF-α*, adiponectin, apolipoprotein C3 impact inducing obesity and nonalcoholic fatty liver in adult Indian population (Jain et al., 2019). Such polymorphisms may also aggravate the chances of acute hepatic failure in orlistat therapy.

3.4 Genetic polymorphism of acute oxalate nephropathy

Parathyroid hormone, a primary regulator of equilibrium in calcium content and an essential manager of its proclamation, is a calcium-sensing receptor *(CaSR)*, a G-protein coupled receptor articulated in the parathyroid gland and renal tubular cells. Its stimulation leads to the elevated excretion of calcium in the kidney, and mutation in the *CaSR* gene has been revealed to act as the source for the irregularities in blood calcium ion (Ca^{2+}) heights (Thorleifsson et al., 2009). The existence of an inactivating and activating mutation of the *CaSR* gene leads to familial hypocalciuric, hypercalcemia or autosomal dominant hypocalcemia correspondingly (Scillitani et al., 2007). The 3 SNPs encrypting the intracellular realm of CaSR by instigating non-conservative amino acid variations have been pronounced on exon 7.

A modern genome-wide association study (GWAS) charted the complete human genome and discovered SNPs in claudin 14 *(CLDN14)* that was muscularly allied with kidney stone. This investigation showed *CLDN14* T>C (rs219780 and rs219781) had elevated the possibility of emerging kidney stones. A tight junction membrane protein CLDN14 is articulated in the epithelia and endothelia and form para-cellular blockades and apertures that regulate constricted junction penetrability (Yao et al., 2005). CLDN14 diminishes the permeability of Ca^{2+} through constricted junctions. Former investigation stated that utterance of CLDN14 is muscularly upregulated by CaSR stimulation and dysregulation of renal CaSR-CLDN14 alley that could come up with the growth of kidney stone (Dimke, et al., 2013). Other side, CLDN14 plays a significant part in the regulating the renal Ca^{2+} excretion and CLDN14 is governed by signaling of CaSR. The

pronouncement of CLDN14 is amplified through stimulating mutation of CaSR gene and leads to nephrocalcinosis (Nuij et al., 2017). Hence, *VDR*, *CaSR* and *CLDN14* are regarded as candidate gene for KSD. In the current investigation, we assess the potential overtone of *VDR*, *CaSR* and *CLDN14* genes in cases with KSD in the eastern part of India. The primary reason for oxalate nephropathy in orlistat therapy is calcium-binding with the free fatty acids. This can increase the oxalate absorption in colon and oxalate crystal urea and nephropathy (Chaudhari et al., 2013). DGKH genetic polymorphisms were studied to identify its effect on oxalate stones. The study results stated that patients with *DGKH* genetic polymorphism are more susceptible to oxalate crystal formation than regular patients. While correlating with the orlistat therapy, the chances of oxalate nephropathy may be more for the patients with *DGKH* genetic polymorphisms (Xu et al., 2014).

Polymorphism in these genes i.e., *SCN54, ATG16L1, PRSS1, SPINK1, CTRC, CTSB, IL, GST, CASP, MIF, PTGS2, ACE, MYO9E, HFE, CaSR, VDR, CLDN14* are more susceptible to an adverse reaction similar to that of adverse effects which may happen during orlistat administration. So, by this approach, we can predict that these polymorphic populations are not suitable candidates for orlistat administration. Being genetic, they are already highly susceptible. Administering orlistat may provoke those medical conditions as adverse events. For further clarity, all the reported medical conditions associated with genetic polymorphisms in different countries are explained in Table 2.

Table 2. susceptible genetic polymorphism for orlistat induced adverse effects

	GENES	DISEASES	FUNCTIONS	REFERENCE
1.	SCN5A	Gastrointestinal	Sodium channels transcription supports in gastrointestinal motility	Adam et al., 2007; Jun et al., 2011; Ek at al., 2015; Franke et al., 2010;
2.	ATG16L 1	Gastrointestinal	Protein synthesis to trigger autophagy by which cell repairing will take place.	Benkirane et al., 2015
3.	PRSS1	Pancreatitis	Cationic trypsinogen enzyme to support digestive breakdown**.**	Yi et al., 2016; Zhang et al., 2017
4.	SPINK1	Pancreatitis	Provides instructions for making trypsin inhibitor, source of secretion acinar cells.	Koistinen et al., 2016;
5.	CTRC	Pancreatitis	Provides instructions for making serum calcium-decreasing factor that has chymotrypsin-like protease activity.	Rosendahl et al., 2008; Paliwal et al., 2013; Koziel et al., 2017.
6.	CTS B	Pancreatitis	Provides instructions for making of the C1 family of peptidases supports protein digestion.	Mahurkar et al., 2006; Weiss et al., 2007
7.	IL	Pancreatitis	provides instructions for making a protein that is involved in immune management	Smithies et al., 2000; Powell et al., 2001;
8.	GST	Pancreatitis	Provides instructions for making glutathione S-transferase (GST)	Rahman et al., 2004

			that catalyze the conjugation of reduced GSH to a variety of electrophilic and hydrophobic substances.	
9.	*CASP*	Pancreatitis	Provides instructions for making of cysteine-aspartic acid protease, caspases plays a central role in the execution-phase of cell apoptosis	Martins et al., 2017;
10.	*MIF*	Pancreatitis	This gene encodes a lymphokine involved in cell-mediated immunity, Immuno-regulation, and inflammation. It plays a role in the regulation of macrophage function in host defense.	Makhija et al; 2007
11.	*PTGS2*	Pancreatitis	Encodes COX-2 converts arachidonic acid (AA) to prostaglandin endoperoxide H2 in inflammation.	Özhan et al., 2010; Chen et al., 2017
12.	*ACE*	Pancreatitis	The conversion of angiotensin I to angiotensin II that acts as a vasoconstrictor by the help of RAS	Fang et al., 2015; James et al., 2015
13.	*MYO9B*	Pancreatitis	Encodes the myosin molecule, helps to maintain the functions of GI mucosa.	Monsuur et al., 2005;; Nijmeijer et al., 2013
14.	*HFE*	Sub-acute hepatic failure	Provides instructions for making the HFE protein which interacts with other proteins on the cell surface to detect the amount of iron in the body.	Pietrangelo et al., 2002;

15.	*CaSR*	Acute oxalate nephropathy	This gene encodes a protein `called calcium-sensing receptor. Calcium molecules attach to the receptor, which helps in monitoring and regulate the amount of calcium in the blood.	Scillitani et al., 2007
16.	*VDR*	Acute oxalate nephropathy	This gene encodes a protein called vitamin D receptor (VDR), which allows the body to respond to vitamin D	Dimke et al., 2013
17.	*CLDN14*	Acute oxalate nephropathy	Provides instructions for making Claudin-14, an integral membrane protein and a component of tight junctions	Thorleifsson et al., 2009; Dimke et al., 2013

4. Conclusion

The orlistat is the conventional FDA-approved drug for the long-term management of obesity, which acts by inhibiting the lipase enzymes and preventing TG's breakdown in the intestine. However, the consumption of orlistat is reported with a vast number of clinical adverse effects such as pancreatitis, sub-acute hepatic failure, and severe hepatic injury, kidney stone, acute oxalate nephropathy, kidney injury, and renal failure, diabetic ketoacidosis, and hypertension. We have appraised the orlistat associate four significant adverse effects that are caused repeatedly in many populations such as GI disorders, pancreatitis, sub-acute hepatic failure, and acute oxalate nephropathy. Further, we have reported mechanism and interventional reports for those adverse effects and extend its possible association with genetic polymorphism. Our analysis highlighted the particular clinically reported genes responsible for the reported disorder susceptibility, similar to the kind of adverse drug reactions caused by orlistat.

According to the literature analysis carried out by Nivya *et al.,* it was found that 5 to 10% of hospitalization was due to adverse events produced by the drug. Among this, 50 % was found to be preventable (Nivya et al., 2015). This preventable ADR can be managed by clinical

monitoring systems, patient advice, and system management (Olivier et al., 2002; Benkirane et al., 2015). However, the good clinical success of a drug includes maximized control of adverse events. It is therefore essential to gain knowledge on gene-derived unpredictable adverse effects. For instance, by analyzing the susceptibility to specific adverse conditions either by genetic or population pharmacokinetics, it would be possible for clinicians and drug developers to provide specific dose for specific gene-related populations, which could lead to a new path of personalized medicine with minimized adverse events. Thus, shortlisting pre-reported ADR and susceptible gene polymorphisms such as *PRSS1, SPINK1, CTRC, GST, CASP, MIF, etc*., and comparing them with orlistat-related ADR of a similar kind, could initiate novel strategies of personalizing orlistat for the specific genotypic population without ADR susceptible gene.

At the right time, the right medicine to the right patient is a globally accepted solution to manage predictable adverse events. It would be even possible to minimize unpredictable adverse events to the maximum extent by considering genetic information. A combined approach of molecular biologists, clinicians, and industrialists can result in cost-effective "genetic prescreening" before medication. This strategy will significantly reduce orlistat-related ADR and enhance the market utility of this molecule for social benefit.

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