

Acetate alleviates glucose dysregulation and atherogenic dyslipidaemia in experimentally induced PCOS

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Abstract

Objective: Polycystic ovarian syndrome (PCOS) is a female reproductive disorder that originates from both endocrine and metabolic disruptions, affecting about 6-21% of women of reproductive age globally. Atherogenic dyslipidaemia refers to alterations in circulating lipid levels, which contribute to cardiovascular and renal complications in PCOS. Acetate, a short-chain fatty acid, has been reported to attenuate endocrine/metabolic complications as well as improve glucose homeostasis; hence, this study was designed to explore the effect of acetate on glucose dysregulation and dyslipidaemia in experimentally induced PCOS.

Methods: Female Wistar rats at eight weeks old were procured and assigned into four groups (n=6): Control (CTL), Letrozole (LET), Acetate (ACT), and LET+ACT. Letrozole (aromatase inhibitor; 1 mg/kg) administration for 3 weeks induced PCOS, and treatment with acetate was by co-administration for 3 weeks, during Letrozole administration.

Results: Rats with PCOS presented hyperandrogenism/hypoestrogenism as observed by elevated levels of testosterone, LH/FSH ratio, with a decrease in 17- β oestradiol and SHBG levels when compared with the negative control group. In addition, PCOS rats showed a significant increase in body and ovarian weight, as well as fasting insulin levels. Similarly, circulating levels of TC, LDL, TC/HDL ratio, IL-6, and LDH were elevated in PCOS rats, with a significant decrease ($p < 0.05$) in HDL and nitric oxide in rats with PCOS when compared with the control group.

Conclusion: The present study revealed that acetate alleviates atherogenic dyslipidaemia and metabolic disturbance in the PCOS animal model.

Keywords: Acetate, Atherogenic dyslipidaemia, Glucose dysregulation, Inflammation, PCOS

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Plain English summary

Polycystic ovarian syndrome (PCOS) is a disorder that affects women of childbearing age, which is considered the main cause of female infertility because of hormonal imbalance. In addition, patients with PCOS may develop disturbed lipid levels, which often progress to other complications, including cardiovascular diseases (CVD). To date, there is no cure for PCOS, however, its symptoms are often managed using medications such as oral contraceptives to regulate the hormonal profile of individuals with PCOS. Nevertheless, these drugs have proven ineffective. Acetate is a product of fermented food in the gut/intestine of an individual that helps in regulating the overall wellness of the body. This present study was designed to investigate the beneficial role of acetate in reversing lipid alterations in the PCOS model.

Background

Polycystic ovarian syndrome (PCOS) is a metabolic and endocrine disorder that is common in 6-21% of women (1, 2) within the ages of 12-50 years (3), and is attributable to about 70-80% of female infertility globally (4). The notable features of PCOS include irregular menstruation, anovulation, androgen excess/male pattern hair distribution, and excess adiposity, among others (5, 6). Although the symptoms of PCOS may be misdiagnosed, as some of the PCOS symptoms share similarities with other metabolic complications, including endometriosis (7), Cushing's syndrome (8), among others. Notwithstanding, it is well documented that Rotterdam criteria are a reliable guideline for the diagnosis of PCOS, which confirms an individual with PCOS when presented with at least two of the three symptoms, including anovulation/oligomenorrhea, androgen excess and polycystic ovaries under ultrasound (9, 10). To date, the aetiology of PCOS remains elusive, hence making treatment of this disorder suboptimal [5]. Previous studies have also reported the detrimental effects of PCOS, including long-term complications such as obesity, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and cardiovascular diseases, among others (11, 12). Nevertheless, insulin resistance (IR) remains a critical feature in PCOS that contributes to the progression of several metabolic complications observed in women who suffer from PCOS.

Insulin resistance (IR) has been well reported in earlier studies, including studies from our laboratory as a critical player in the manifestation of metabolic disorders, as its presence alters the function of metabolic tissue, including adipocytes, thereby leading to lipolysis/depletion in adipose storage and contributing to increased circulation of triglyceride, low density lipoprotein cholesterol (LDLc), with a consequent decrease in high-density lipoprotein cholesterol (HDLc) (13, 14, 15, 16). Atherogenic dyslipidaemia refers to an excessive increase in circulating levels of triglyceride, cholesterol, LDLc, depleted level of HDLc, as well as elevated TC/HDLc ratio, which is an

atherosclerotic marker, thus contributing to heart failure, myocardial infarction, and endothelial dysfunction, among others (17, 18). Similarly, lipolysis causes an influx of inflammatory cytokines, an increase in reactive oxygen species and a subsequent depletion in the antioxidant system, thus promoting oxidative stress, which precedes ventricular dysfunction (19, 20, 21). According to the World Health Organisation, 18% of ischemic heart disease and 56% of stroke are attributable to atherogenic dyslipidaemia, contributing to the increased death rate, attributed to cardiovascular disease globally (22). Hence, atherogenic dyslipidaemia remains an independent risk factor for CVD, and patients with dyslipidaemia/hyperlipidaemia, as observed in metabolic disorders including PCOS, are more likely to develop cardiovascular complications (23, 24).

Short-chain fatty acids (SCFAs) are essential gut metabolites derived from fermented dietary fibres that act as key mediators of metabolic health, as well as overall wellness (25). There are several SCFAs synthesised in the gut, however, three of these are well recognised in circulation, which include acetate, butyrate and propionate (26, 27, 28). Acetate, which is the most abundant SCFA in circulation, has gained much attention as a therapeutic agent in reversing metabolic alterations due to its anti-lipolytic, anti-inflammatory, anti-oxidative and anti-fibrotic/-apoptotic properties (29, 30, 31). Several studies, including studies from our laboratory have reported that SCFA, particularly acetate elicit its positive role by interacting with several metabolic pathways that regulate cellular activities, including via modulation of combination of G-protein coupled receptors 41 and 43 (GPCR41/43) or inhibition of histone deacetylases (HDACs) (16, 27, 32, 33). In addition, it has also been reported that acetate reversed PCOS-associated cardiometabolic disorder via suppression of the PCSK9/NF-kb-dependent pathway, although this mechanism is still under elucidation (18). However, the present study was designed to investigate the beneficial effect of

acetate on glucose dysregulation and atherogenic dyslipidaemia in experimentally induced PCOS.

Methods

Experimental animals and grouping

This study was conducted following the National Institutes of Health Guide for the Care and Use of Laboratory Animals, while the research was reported following ARRIVE 2.0 guidelines. Eight-week-old female Wistar rats were procured and housed in the Institution's animal house, respectively. Rats had unrestricted access to standard rat chow and tap water. The protocol was approved by the Ethical Review Board of Afe Babalola University (Ado-Ekiti, Nigeria), and every effort was made to minimise both the number of animals used and their suffering. All the animals chosen for the work were with at least three sequential regular oestrous cycles and on the same oestrous stage, as determined via vaginal cytology for each rat. After 2 weeks of acclimatisation, the animals were randomly assigned into four groups ($n=6$ per group), namely: Control, acetate-treated (ACT), letrozole (LET), and LET + ACT-treated groups. Rats were maintained in a colony under standard environmental conditions of temperature (22-26°C), relative humidity (50-60%), and a 12-hour dark/light cycle.

Induction of PCOS

Rats were given letrozole (1 mg/kg) for 21 days consecutively to induce experimental PCOS as previously described (34, 35).

Treatment

Distilled water was given (vehicle) by oral gavage to the control and LET groups, ACT and LET + ACT groups received 200 mg/kg (oral gavage) of sodium acetate (Sigma-Aldrich, St Louis, MI), The treatments were done simultaneously and uninterruptedly for 21 days (18, 36).

Metabolic indices

The glucose tolerance test was performed 48 hours before the sacrifice of the rats. After a 12-h overnight fast, basal blood glucose was determined, and the rats were loaded with glucose (2 g/kg; oral gavage). The blood was obtained sequentially at 30, 60, 90 and 120 minutes and was recorded. Blood glucose levels were monitored with a hand-held glucometer (ONETOUCH@-LifeScan, Inc., Milpitas, CA, USA).

Collection of samples

At the end of the treatment, the rats were anaesthetised by intraperitoneal injection of sodium pentobarbital (50 mg/kg). Blood was collected by cardiac puncture into a heparinised tube and centrifuged at 704 g for 5 min at room temperature. Plasma was stored frozen until it was needed for biochemical assay.

Biochemical analysis

Plasma endocrine profile

Plasma insulin concentration was determined with Rat ELISA kits obtained from Calbiotech Inc. (Cordell Ct., El Cajon, CA 92020, USA), and the manufacturer's procedures were followed. The plasma testosterone, sex hormone binding globulin (SHBG), and 17- β oestradiol were determined with Rat ELISA kits obtained from Calbiotech Inc. (El Cajon, USA) by following the manufacturer's assay procedure.

Plasma lipid profile and inflammatory biomarkers

Standard colourimetric methods using assay kits obtained from Fortress Diagnostics Ltd. (Antrim, UK) were used to determine the total cholesterol (TC), high-density lipoprotein-cholesterol (HDLc), and low-density lipoprotein cholesterol (LDLc) from the plasma. Besides, plasma TC/HDLc was determined as an atherogenic lipid marker (18, 37).

Plasma nitric oxide

Nitric oxide concentration was determined in the plasma by a standard spectrophotometric method using kits from Oxford Biomedical Research Inc. (Oxford, UK) and in line with the manufacturer's guidelines.

Data analysis and statistics

The data distribution was confirmed using the Shapiro-Wilk test, and the data were normally distributed. All data were expressed as means \pm S.D. Statistical group analysis was performed with GraphPad Prism software version 5. One-way ANOVA was used to compare the mean values of variables among the groups; thereafter, Bonferroni's *post hoc* analysis was applied. Statistically significant differences were considered at p less than ($<$) 0.05.

Results

Acetate reverses increased body and ovarian weight in the PCOS rat model

Animals with PCOS were presented with a significant increase ($p<0.05$) in ovarian and body weight compared to the control animals. However, animals that received supplemented treatment with

acetate showed a significantly reduced ($p < 0.05$) body and ovarian weight compared to the untreated PCOS group (Table 1).

Table 1: Effects of sodium acetate on ovarian weight (a) and body weight (b) in LET-induced PCOS

GROUPS	CONTROL	ACT	LET	LET+ACT
Ovarian weight (g)	0.29 ± 0.02	0.28 ± 0.03	0.57 ± 0.07*	0.31 ± 0.03 [#]
Body weight change (g)	19.75 ± 1.27	19.2 ± 2.12	38.5 ± 0.74*	22.33 ± 1.85 [#]

Values are expressed as mean ± S.D. n=6. (* $p < 0.05$ vs control; [#] $p < 0.05$ vs LET). Control (CTL), sodium acetate (ACT), letrozole (LET), letrozole + sodium acetate (LET+ACT)

Acetate regulates glucometabolic indices in the PCOS rat model

The circulating insulin levels of animals with PCOS were significantly elevated ($p < 0.05$), while no significant difference in blood glucose was observed in PCOS animals compared to control

animals. Nevertheless, the plasma level of animals treated with acetate was significantly reduced ($p < 0.05$), while there was no significant change in blood glucose level compared to untreated PCOS animals (Figure 1).

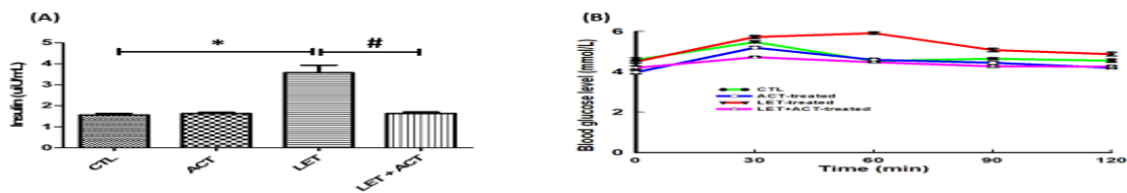


Figure 1: Effects of sodium acetate on fasting insulin (a) and glucose tolerance (b) in LET-induced PCOS
 Values are expressed as mean ± S.D. n=6. (* $p < 0.05$ vs control; [#] $p < 0.05$ vs LET). Control (CTL), sodium acetate (ACT), letrozole (LET), letrozole + sodium acetate (LET+ACT)

Acetate abates hormonal dysregulation in the PCOS rat model

Plasma concentration of Testosterone and LH/FSH ratio were significantly elevated ($p < 0.05$), while 17β-oestradiol and SHBG were reduced in PCOS animals compared to control animals. However, in

animals that received supplemented treatment with acetate, the plasma concentrations of testosterone and LH/FSH were significantly reduced ($p < 0.05$), while the concentration of 17β-oestradiol and SHBG were elevated when compared to the control group (Table 2).

Table 2: Effects of sodium acetate on testosterone (a), 17β-oestradiol (b), LH/FSH ratio (c), and SHBG (d), in LET-induced PCOS

GROUPS	CTL	ACT	LET	LET +ACT
Testosterone (ng/mL)	0.26 ± 0.11	0.24 ± 0.10	2.66 ± 0.51*	0.13 ± 0.05 [#]
17-β estradiol (ng/mL)	5.03 ± 0.40	4.77 ± 0.52	1.71 ± 0.26*	4.63 ± 0.84 [#]
LH/FSH ratio	18.58 ± 0.83	16.99 ± 0.53	34.03 ± 3.91*	17.66 ± 0.63 [#]
SHBG (pg/mL)	530.80 ± 3.23	548.8 ± 10.53	246.5 ± 12.29*	428.30 ± 18.39 [#]

Values are expressed as mean ± S.D. n=6. (* $p < 0.05$ vs control; [#] $p < 0.05$ vs LET). Control (CTL), sodium acetate (ACT), letrozole (LET), letrozole + sodium acetate (LET+ACT), 17-beta oestradiol (17-B oestradiol), luteinising hormone/follicle stimulating hormone (LH/FSH) ratio, sex hormone binding globulin (SHBG)

Acetate attenuates lipid alterations in the PCOS rat model

The plasma concentrations of TC, TC/HDLc and LDLc were significantly increased ($p < 0.05$), while the concentration of HDLc was depleted in PCOS animals compared to the control group.

Nevertheless, supplementation with acetate significantly decreased ($p < 0.05$) the concentrations of TC, TC/HDLc and LDLc, and increased the concentration of HDLc in treated animals compared to the untreated group (Figure 2).

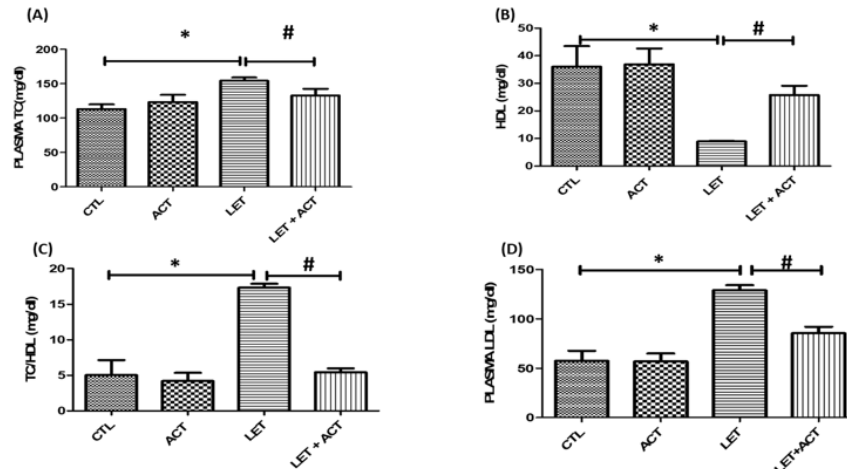


Figure 2: Effects of sodium acetate on TC (a), HDL (b), TC/HDLc (c), and LDLc (d) in LET-induced PCOS Values are expressed as mean \pm S.D. $n=6$. (* $p < 0.05$ vs control; # $p < 0.05$ vs LET). Control (CTL), sodium acetate (ACT), letrozole (LET), letrozole + sodium acetate (LET+ACT), total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDLc), low-density lipoprotein cholesterol (LDLc)

Acetate regulates the inflammatory response and nitric oxide in the PCOS model

There was a significant increase ($p < 0.05$) observed in the IL-6 level, while a notable decrease in nitric oxide level was observed in animals that developed PCOS when compared to the control animals.

Nonetheless, it was observed that IL-6 levels were significantly reduced ($p < 0.05$), and nitric oxide level was elevated in animals that received supplemented treatment with acetate compared to the untreated PCOS group (Figure 3).

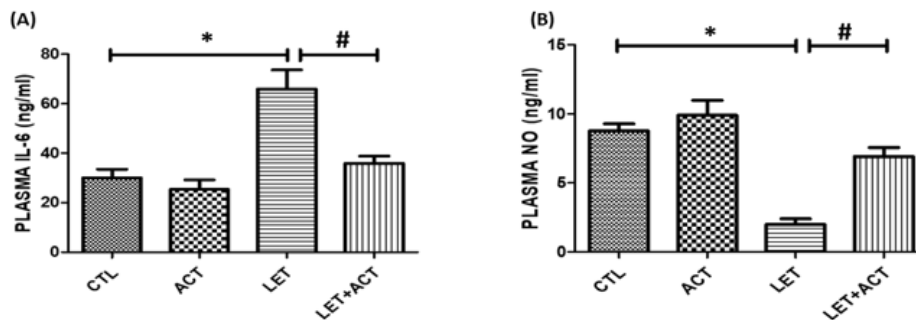


Figure 3: Effects of sodium acetate on IL-6 (ng/mL) (a), NO (ng/mL) (b) in LET-induced PCOS. Values are expressed as mean \pm S.D. $n=6$. (* $p < 0.05$ vs control; # $p < 0.05$ vs LET). Control (CTL), sodium acetate (ACT), letrozole (LET), letrozole + sodium acetate (LET+ACT), interleukin-6 (IL-6), nitric oxide (NO)

Discussion

The findings from this study revealed that animals with PCOS were characterized with increased body/ovarian weight, altered glucose regulation (elevated levels of plasma insulin, insulin resistance/elevated circulating glucose at 60 mins

post-load glucose), hyperandrogenism (as observed by elevated levels of testosterone, LH/FSH ratio, as well as reduced level of testosterone clearance (SHBG) and circulating 17-B oestradiol). In addition, it was observed that the lipid profile of animals with PCOS was disrupted,

and this was observed by a significant increase in the circulating levels of TC, TC/HDL ratio, and LDLc, with a significant decrease in plasma HDLc when compared with control animals. Similarly, increased inflammatory response (Interleukin-6) and lactate dehydrogenase concentration were shown in PCOS animals, as well as a depleted nitric oxide level. Nevertheless, supplementation with acetate reversed these morphological, hormonal, and lipid alterations as well as suppressed the inflammatory response in treated PCOS animals compared with the untreated PCOS group.

The present study revealed that animals with PCOS developed altered glucose metabolism/insulin resistance as observed by elevated levels of plasma insulin and hyperinsulinemia/insulin resistance at 60 minutes post-load glucose when compared with control animals. This present finding is a validation of previous studies, including studies from our laboratory, which described glucose dysregulation/insulin resistance as a critical feature of PCOS (18, 33, 38, 39). In addition, findings from this present study revealed an increase in plasma testosterone and LH/FSH ratio, while a decrease in 17 β -oestradiol and SHBG concentration in PCOS animals when compared with control animals. The presence of hyperinsulinemia/IR has been reported to contribute significantly to increased concentration of testosterone in women [39, 40]. Insulin resistance has been implicated in the disruption of GnRH pulsatility (LH and FSH stimulation), thus promoting the release of LH over FSH as observed by increased LH/FSH ratio and thus enhancing the production of excess androgens (testosterone) with a consequent suppression in the circulating level of 17-B oestradiol as observed in this present study. Similarly, SHBG, which clears testosterone from circulation (35, 41, 42), was decreased in PCOS animals, showing that the reduced plasma clearance of testosterone contributed to an increased level of testosterone in PCOS animals compared to control animals, as observed in this study. Nevertheless, animals that were treated with acetate showed improved glucose regulation and homeostasis in PCOS animals, thus validating the glucoregulatory/metabolic effect of SCFA, particularly acetate. In addition, it was also observed that acetate attenuated hormonal imbalance in PCOS animals, as observed by reduced level of testosterone and LH/FSH ratio, as well as improved circulating levels of 17-B oestradiol and testosterone clearance (SHBG) when compared with the untreated PCOS group,

thus suggesting the therapeutic potential of acetate in modulating hormonal profile in PCOS model. These findings are in consonance with our earlier findings (18, 30).

In the present study, PCOS animals also demonstrated elevated levels of lipids (plasma TC, TC/HDLc, and LDLc), which is an indication of dyslipidaemia. Lipid dysregulation is a feature of insulin resistance, a critical player in the progression of metabolic syndrome and obesity (13, 14, 15, 16), validating the manifestation of metabolic disorders in PCOS individuals. More so, it was observed that the TC/HDLc ratio was significantly increased in PCOS animals compared to control animals. Previous studies have reported that TC/HDLc, an atherosclerotic marker, plays a critical role in the progression of cardiovascular diseases by the formation of atherosclerotic plaques in blood vessels of vital organs, including the cardiac muscle, thereby restricting blood flow to these organs and contributing to the risk of cardiovascular diseases (17, 18), implying that individuals with dyslipidaemia/hyperlipidaemia (23, 24), as observed in this study, are more likely to develop cardiovascular disease risks. Notwithstanding, treatment with acetate averted dyslipidaemia and atherosclerotic events in PCOS animals, thus revealing the anti-lipidemic effect of acetate in metabolic-related disorders, especially PCOS.

Our result also revealed elevated levels of inflammatory response (IL-6), with nitric oxide (NO) depletion in PCOS animals compared with controls. Several studies, including findings from our laboratory, have demonstrated that dyslipidaemia triggers an inflammatory response (35, 43, 44), which was validated in this study by elevated levels of IL-6 in animals that developed PCOS when compared to control animals. Excessive inflammatory response has been demonstrated to aggravate cellular inflammation which significantly compromises the antioxidant system, thus contributing to elevated expressions of reactive oxygen species (ROS) and oxidative stress which precedes several complications attributable to metabolic disorders including myocardial infarction, ventricular dysfunction, among others (19, 20, 21), and this could progress to cellular damage/apoptosis. Nonetheless, treatment with acetate suppressed the inflammatory response and significantly improved the synthesis of nitric oxide in PCOS animals when compared to untreated PCOS animals, which implies that treated PCOS animals are more likely to be protected from cardiovascular risks compared to untreated PCOS animals. In addition, the

present finding supports previous reports on the anti-inflammatory and anti-oxidative effects of acetate in metabolic disorders (29, 30, 31), including in PCOS. Interestingly, the present data possibly provides a preclinical relevance in the management of atherosclerosis and metabolic disorders, which underlie PCOS pathogenesis, thus suggesting a potential therapy for PCOS.

Conclusion

The present study revealed that SCFA, acetate, alleviates atherogenic dyslipidaemia and metabolic disturbance in the PCOS animal model.

List of Abbreviations

ACT: Acetate
ANOVA: Analysis of variance
CON: Control
ELISA: Enzyme-linked immunosorbent assay
FSH: Follicle-stimulating hormone
GnRH: Gonadotropin-releasing hormone
GPCR 41&43: G-protein coupled receptors 41and43
HDACs: Histone deacetylases
HDLc: High-density lipoprotein cholesterol
IL-6: Interleukin-6
IR: Insulin resistance
LDLc: Low-density lipoprotein cholesterol
LET: Letrozole
LH: Luteinizing hormone
NF-kB: Nuclear factor kappa B
NO: Nitric oxide
p.o.: per ostium
PCOS: Polycystic ovarian syndrome
PCSK9:Proprotein subtilisin kexin type 9
ROS: Reactive oxygen species
SCFAs: Short-chain fatty acids
S.D.: Standard deviation
SHBG: Sex hormone binding globulin
TC: Total cholesterol

Declarations

Ethics approval and consent to participate

The protocol was approved by the Ethical Review Board of Afe Babalola University (Ado-Ekiti, Nigeria), and every effort was made to minimise both the number of animals used and their suffering. Consent to participate is not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data supporting the present study will be made available on request from the corresponding author.

Conflicting interests

The authors have no conflict of interest to declare.

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Authors' contributions

ASE and OKS conceived, designed and conducted the experiment. UJN, AA, OCA, ECF, ACL, ACO, OGO, OSO, AOE, AIO, AMB, BOC, OOA, AK, OPA, and SOA contributed reagents. ASE, UJN, AA, OCA, ECF, ACL, ACO, OGO, OSO, AOE, AIO, AMB, BOC, OOA, AK, OPA, SOA, and OKS reviewed, revised and approved the final manuscript for submission.

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