

**A Novel Composition With
Ovarian Maintenance
Function and Application
Targeting Cell Genes and
Gut Microbiota**

Ovarian Health



Ovarian Dysfunction



Current Therapies



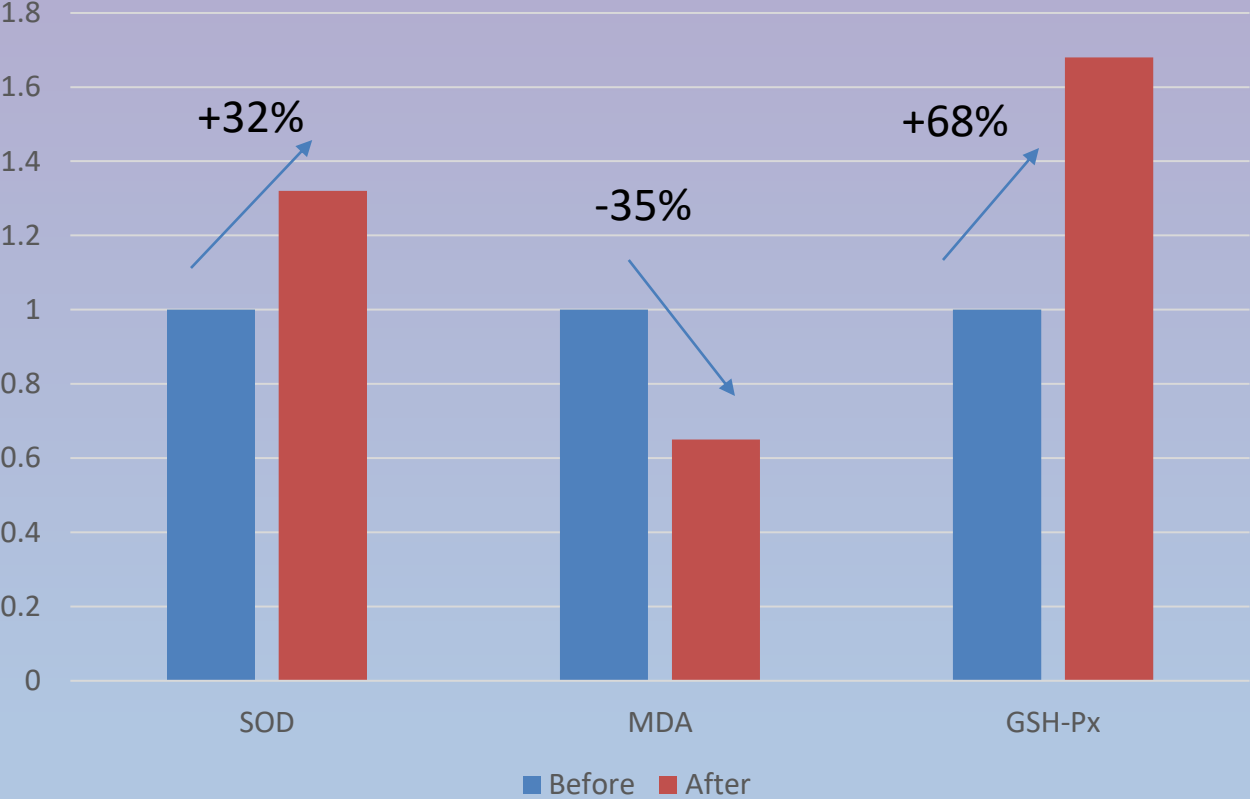
A Composition with Ovarian Maintenance Function



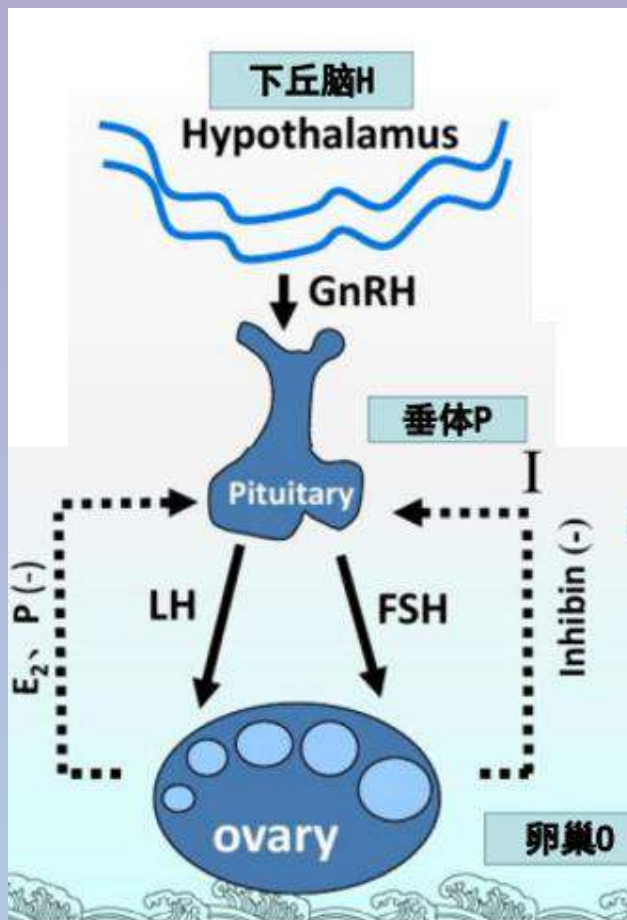
Anti-oxidant Capacity for Ovarian Tissues



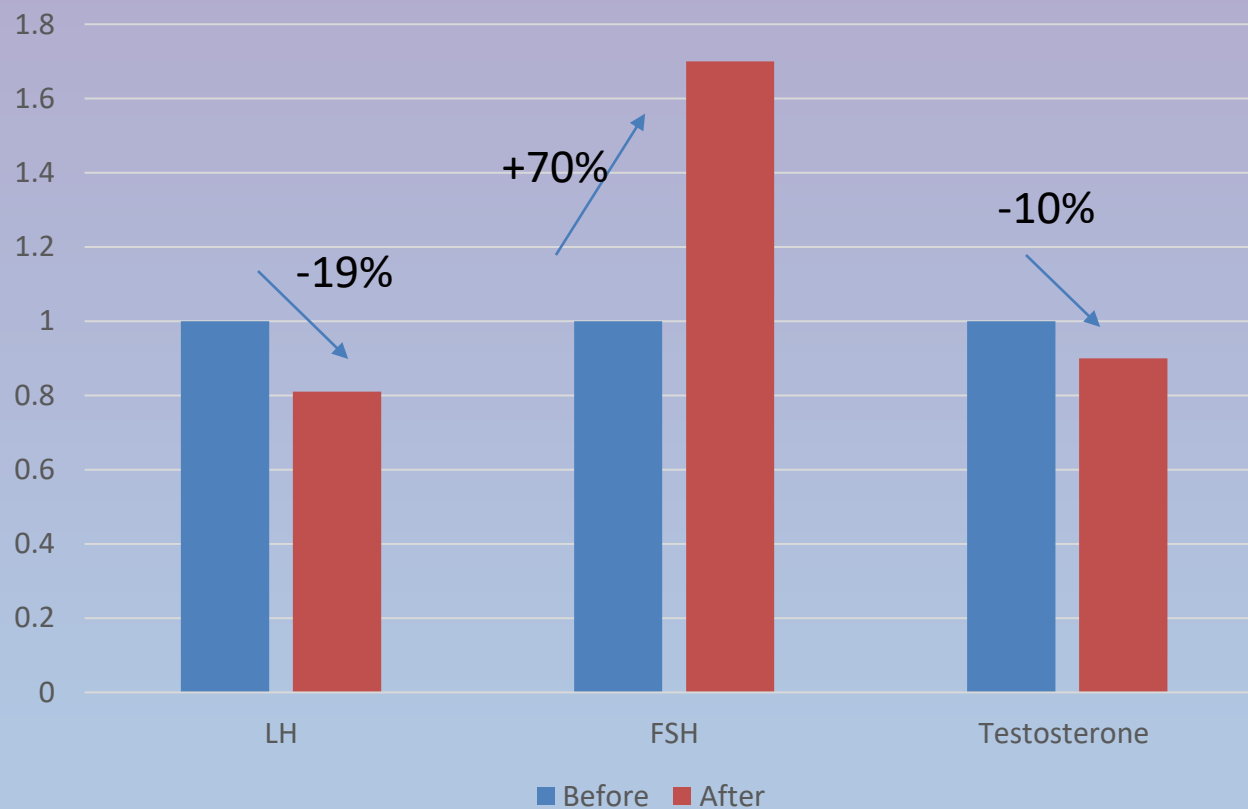
Change of Gene Expressions of SOD, MDA and GSH-Px



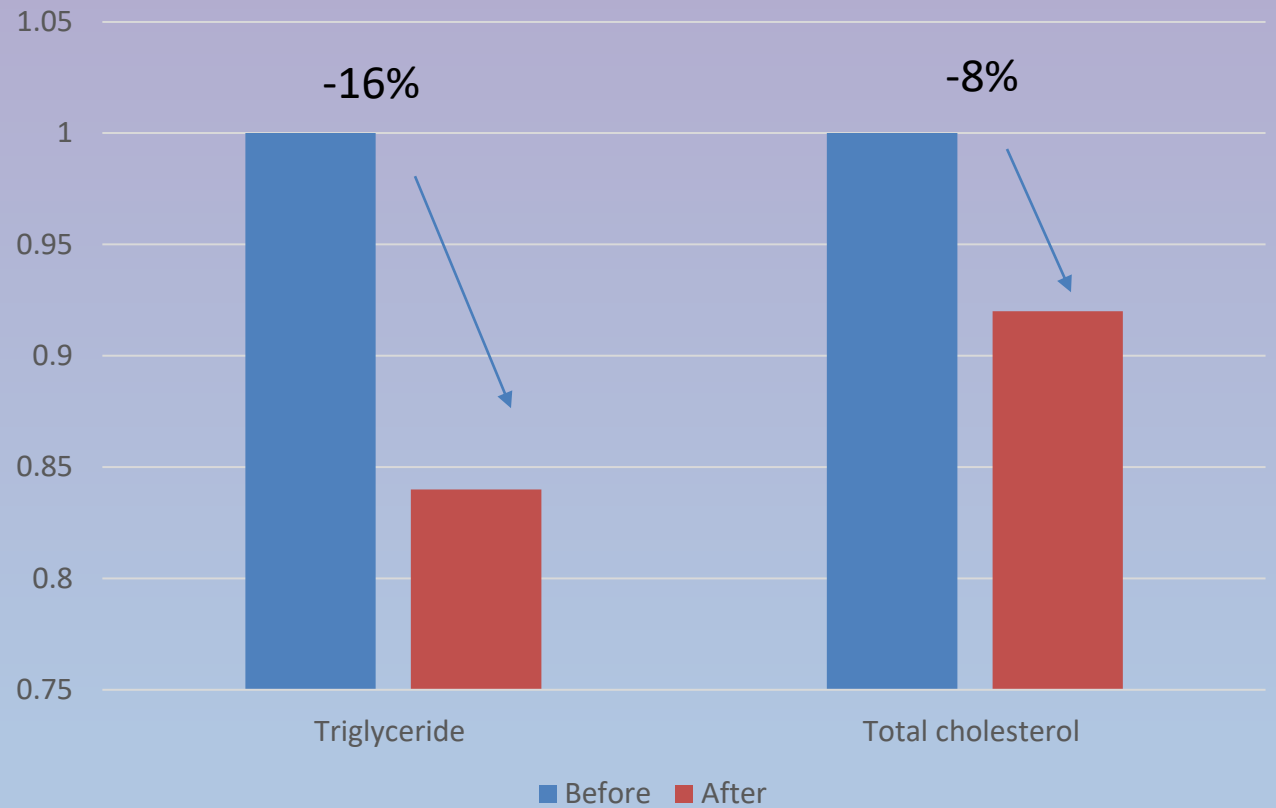
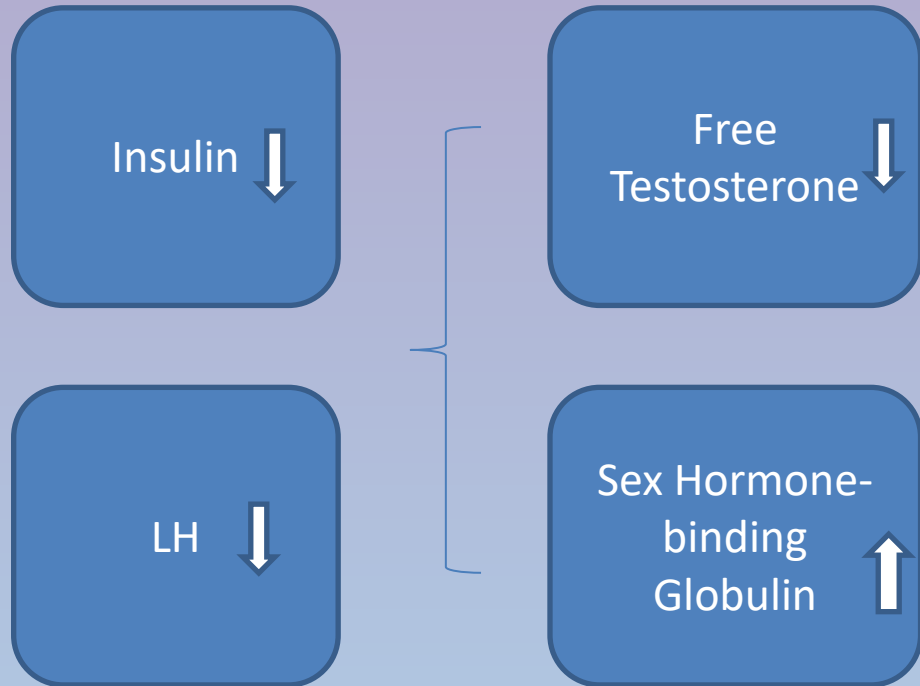
Alleviation for PCOS Symptoms



Change of Gene Expressions of LH, FSH and Testosterone



Improvement on Insulin Sensitivity



Effect on Gut-Ovary Axis

nature
medicine

LETTERS

https://doi.org/10.1038/s41591-019-0506-0

Gut microbiota-bile acid-interleukin-22 axis orchestrates polycystic ovary syndrome

Xinyu Qi^{1†}, Chuyu Yun^{1,2†}, Lulu Sun^{1,2}, Jialin Xia^{1,2}, Qing Wu^{1,2}, Ying Wang^{1,3,4}, Lina Wang^{1,4,5}, Yangming Zhang^{1,2}, Xianyi Liang^{1,2}, Liying Wang^{1,4,5}, Frank J. Gonzalez^{6,7}, Andrew D. Patterson^{8,9}, Huiying Liu^{1,2}, Liangshan Mu^{1,2}, Zehong Zhou^{1,2}, Yue Zhao^{1,2}, Rong LF^{1,2,4,7}, Ping Liu^{1,2,4,7}, Chao Zhong¹, Yanli Pang^{1,2,7*}, Changtao Jiang^{1,2*} and Jie Qiao^{1,2,4,7,8,9,10*}

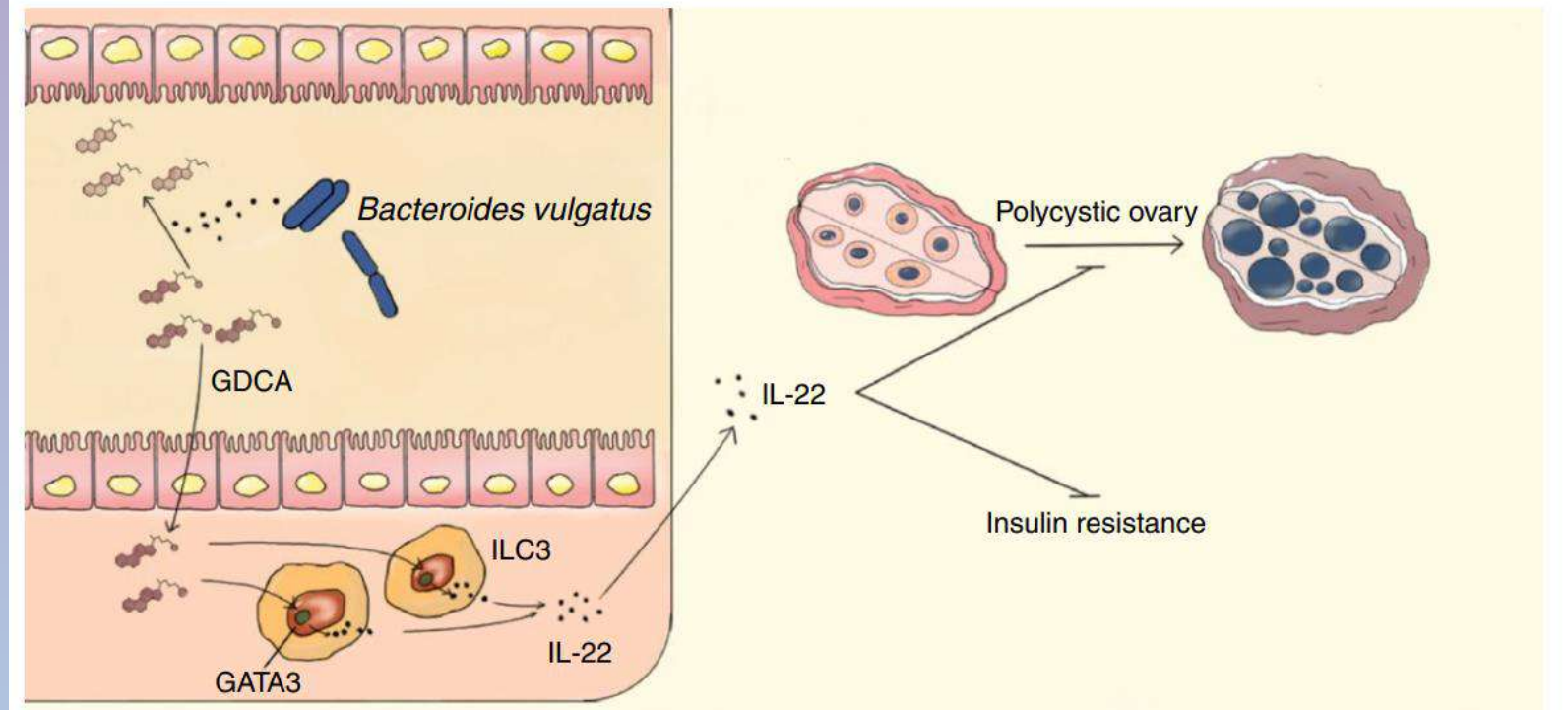
Polycystic ovary syndrome (PCOS) is characterized by androgen excess, ovulatory dysfunction and polycystic ovaries, and is often accompanied by insulin resistance. The mechanism of ovulatory dysfunction and insulin resistance in PCOS remains elusive, thus limiting the development of therapeutic. Improved metabolic health is associated with a relatively high microbiota gene content and increased microbial diversity¹. This study aimed to investigate the impact of the gut microbiota and its metabolites on the regulation of PCOS-associated ovarian dysfunction and insulin resistance. Here, we report that *Bacteroides vulgatus* was markedly elevated in the gut microbiota of individuals with PCOS, accompanied by reduced glycochenodeoxycholic acid and taurochenodeoxycholic acid levels. Transplantation of fecal microbiota from women with PCOS or *B. vulgatus*-colonized recipient mice resulted in increased disruption of ovarian functions, insulin resistance, altered bile acid metabolism, reduced interleukin-22 secretion and infertility. Mechanistically, glycochenodeoxycholic acid induced intestinal group 3 innate lymphoid cell IL-22 secretion through GATA binding protein 3, and IL-22 in turn improved the PCOS phenotype. This finding is consistent with the reduced levels of IL-22 in individuals with PCOS. This study suggests that modifying the gut microbiota, altering bile acid metabolism and/or increasing IL-22 levels may be of value for the treatment of PCOS.

Recent studies showed that individuals with polycystic ovary syndrome (PCOS) have gut microbiota communities different from those of healthy controls^{2–4}. However, due to small sample sizes or racial/ethnic differences among the studies investigating the microbiota in women with PCOS, the community structure and function of the gut microbiota in Chinese individuals with PCOS remains obscure. Importantly, the role and mechanism of the gut microbiota in the pathogenesis and complications of PCOS is largely unknown. To investigate changes in the gut microbiota community structure in individuals with PCOS, 43 healthy control donors and 50 individuals with PCOS were recruited. Body mass index-matched

women with PCOS and control donors were enrolled to delineate the effect of obesity on the gut microbiota and bile acid profiles in individuals with PCOS. Age and waist to hip ratios were not different between the two groups. Individuals with PCOS had significantly higher fibrosis scores (Ferriman-Gallwey score), serum luteinizing hormone levels, luteinizing hormone-releasing hormone-stimulating hormone (FSH) ratios, testosterone levels, androstenedione levels, free androgen index values, dehydroepiandrosterone (DHEA) sulfate levels, triglyceride levels and low-density lipoprotein cholesterol levels, as well as lower levels of serum FSH, sex hormone-binding globulin (SHBG) and high-density lipoprotein cholesterol, compared with healthy controls. Fasting insulin levels and the insulin resistance index (homeostatic model assessment of insulin resistance (HOMA-IR)) were significantly higher in women with PCOS (Supplementary Table 1).

Whole-genome shotgun sequencing showed no significant difference in bacterial alpha diversity between individuals with PCOS and healthy controls (Extended Data Fig. 1a). Notably, the beta diversity of PCOS microbiomes was significantly decreased compared with that of healthy controls, indicating a more homogeneous community structure among individuals with PCOS (Extended Data Fig. 1b). Partial least squares discriminant analysis (PLS-DA) showed that there was a distinct clustering pattern between samples from individuals with PCOS and healthy controls (Fig. 1a). The variable importance in projection (VIP) score for the gut microbiota showed that *Bacteroides vulgatus* contributed significantly to the group separation (Fig. 1b). Furthermore, the abundance of *B. vulgatus* was markedly increased in individuals with PCOS compared with healthy controls (Fig. 1c and Extended Data Fig. 1c,d).

The gut microbiota participates in host metabolism by interacting with host signaling pathways^{5,6}. Kyoto Encyclopedia of Genes and Genomes analysis indicated that bile acid metabolism was one of the key metabolic pathways affected by the gut microbiota changes found in individuals with PCOS (Fig. 1d). Qualitative and quantitative analysis of bile acid species indicated



¹Department of Obstetrics and Gynecology, Center for Obesity and Metabolic Disease Research, School of Basic Medical Sciences, Tsinghua Hospital, Peking University, Beijing, China. ²Department of Pathophysiology, School of Basic Medical Sciences, Peking University, and the Key Laboratory of Molecular Cardiovascular Science, Ministry of Education, Beijing, China. ³Key Laboratory of Assisted Reproduction (Peking University), Ministry of Education, Beijing, China. ⁴National Clinical Research Center for Obstetrics and Gynecology, Beijing, China. ⁵Laboratory of Metabolism, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. ⁶Center for Molecular, Biotechnology and Cancerogenetics, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, University Park, PA, USA. ⁷Beijing Key Laboratory of Reproductive Endocrinology and Assisted Reproductive Technology, Beijing, China. ⁸Institute of System Biomedicine, School of Basic Medical Sciences, Peking University Health Science Center, Beijing Key Laboratory of Tumor Systems Biology, Beijing, China. ⁹Beijing Advanced Innovation Center for Genomics, Beijing, China. ¹⁰Peking-Tsinghua Center for Life Sciences, Peking University, Beijing, China. *These authors contributed equally: X. Qi, C. Zhong, Y. Pang, Changtao Jiang, Jie Qiao. [†]Equal contributors. [✉]e-mail: yanli.pang@bjmu.edu.cn; jiangchao@bjmu.edu.cn; jie.qiao@bjmu.edu.cn

European Patent



Rijksdienst voor Ondernemend
Nederland

> Retouradres Postbus 10366 2501 HJ Den Haag

AANTEKENEN
Ir. W.J.J.M. Kempes
Doglio Patents
Postbus 2350
1200 CJ Hilversum
Nederland

**Octrooicentrum Nederland,
aandiel van Rijksdienst
voor Ondernemend
Nederland**
Octrooien, valorisatie en
Sectoren
Prinsak Beethovelaan 2
2350 AL Den Haag
Postbus 10306
2003 HJ Den Haag
www.vno.nloctrooien

RIC Bank
IBAN: NL41INGR0705001296
BICSWF333INGB2A

Contactpersoon
Team Verlening
T: 06881 042 63 33
teamverlening@vno.nl

Onze referentie
OREZ/2034555A.001

Uw referentie
113-009-20

Datum 17/04/2023
Betreft: Ontvangstbewijs

Octrool(aanvraag) 2034555
ten name van:
ETERNAL GRACE PTE. LTD. te Singapore, Singapore

Geachte lezer,

Octrooicentrum Nederland heeft uw aanvraag om octrooi ontvangen en er de volgende indieningsdatum en het volgende octroolaanvraagnummer aan toegekend:
Indieningsdatum: 12/04/2023
octroolaanvraagnummer: 2034555

Bijgevoegd vindt u een afdruk van de door u aangemelde gegevens, zoals door Octrooicentrum Nederland verwerkt.


In aanvulling op deze brief ontvangt u hetzij bijgaand, hetzij op korte termijn, nóg een bericht.

- Wanneer geen vormgebreken worden vastgesteld in de octroolaanvraag, ontvangt u een bevestiging dat de aanvraag in behandeling wordt genomen.
- Wanneer vormgebreken worden vastgesteld in de octroolaanvraag, ontvangt u daar een overzicht van met een termijn waarbinnen deze gebreken moeten zijn opgeheven.

Ontvangt u geen bericht? Neemt u dan contact op met Octrooicentrum Nederland.

Met vriendelijke groet,

*De directeur van Octrooicentrum Nederland,
namens deze:
Alex Farla
medewerker team Octrooiregister
Dit bericht is automatisch gegenereerd en bevat daarom geen handtekening.*



Overzicht geregistreerde gegevens bij indiening

Aanvraagnummer	: 2034555	Ingediend:	12/04/2023
VNO soort	: Nieuwheidsonderzoek- Nationaal	Ingediend:	12/04/2023
Korte aanduiding	: COMPOSITION WITH OVARIAN MAINTENANCE FUNCTION AND APPLICATION THEREOF		
Tenaamstelling	: ETERNAL GRACE PTE. LTD. te Singapore, Singapore		
Aanvrager(s)	: ETERNAL GRACE PTE. LTD. 128 Tuas South Ave 3, #01-05 637370 Singapore Singapore		
Uitvinder(s)	: Maowa Li Singapore Singapore Jingjing Dai Singapore Singapore		
Gemachtigde	: Ir. W.J.J.M. Kempes Doglio Patents Postbus 2350 1200 CJ Hilversum Nederland		

Pagina 2 van 2

From Science to Product





THANKS
