Research Square

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Analysis of the Effect of Phototherapy on Intestinal Probiotics and Its Metabolism in Newborns With Jaundice

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Abstract

Background: Both long-term and short-term side effects of phototherapy are being increasingly recognized by clinicians. The purpose of this article is to study the changes of intestinal probiotics and their metabolic indexes in newborns with jaundice receiving phototherapy.

Method: Intestinal flora and metabolic changes in newborns were studied through macrogene sequencing and metabonomics.

Results: We found that Bifidobacterium is the main probiotic strain present in the newborn intestinal tract, along with a small amount of Lactobacillus. Both Bifidobacterium and Lactobacillus decreased significantly ($p<0.05$) in neonatal intestinal flora after phototherapy for 24 hours and 48 hours. A correlation analysis between changed probiotics and intestinal short-chain fatty acid metabolites after phototherapy showed that acetic acid, butyric acid, caproic acid, and propionic acid decreased; these metabolites were significantly correlated with Bifidobacterium ($p<0.05$). After phototherapy, non-targeted metabolites also changed significantly ($p<0.05$) and were correlated with many probiotics ($p<0.05$). Significantly changed probiotics demonstrated a significant correlation with some intestinal non-targeted metabolites ($p<0.05$).

Conclusion: Phototherapy can significantly affect the intestinal probiotic flora and its metabolic indicators in newborns with jaundice, which may contribute to phototherapy side effects. These findings also provide a theoretical basis for administering suitable probiotics to newborns with jaundice.

Background

Neonatal hyperbilirubinemia is a common clinical malady caused by excessive bilirubin production *in vivo*, the liver's inability to sufficiently absorb and combine bilirubin, increased intestinal-liver circulation, and abnormal bilirubin excretion, ultimately presenting clinically as neonatal jaundice[1]. About 80% of full-term infants and 90% of premature infants may have jaundice of varying degrees during the early postnatal period. While neonatal jaundice is primarily mild to moderate, it can be severe in some cases. For example, bilirubin encephalopathy can occur when high levels of unbound bilirubin are present in the body and pass through the blood-brain barrier, causing permanent damage if left untreated.

Phototherapy, which can change the structure of bilirubin and increase its excretion, is currently the standard treatment for pathological jaundice[2–3]. Even so, both long-term and short-term side effects of phototherapy are being increasingly recognized by clinicians, such as altered intestinal flora. As such, clinicians often administer oral probiotics to newborns receiving phototherapy to combat these deleterious effects[4]. Because many of these oral probiotics are not well-researched, clinicians tend to rely on their own preferences and experience. For this reason, we used macrogene sequencing to analyze probiotic bacteria changes in the neonatal intestinal tract following phototherapy, and used metabonomics to analyze the correlation between the changes of probiotic strains and metabolism, so as

to provide a theoretical basis for administering probiotics to newborns with jaundice receiving phototherapy.

Methods

1. Clinical subjects: We selected newborns with jaundice who needed phototherapy treatments in the East Hospital of Shanghai Sixth People's Hospital from June 2018 to June 2020 for this study. Only neonates receiving pure artificial feeding were selected for the study. All the clinical information of newborns was recorded.

2. Phototherapy: Each newborn was placed in a blue light treatment box (model XHZ, Ningbo David Medical Devices Co., Ltd.) for phototherapy treatments, which are 425–475 nm in wavelength. The newborn's eyes were covered with a phototherapy eye mask (Foshan forssman Medical Technology Co., Ltd., Yueshun Xiebei No. 20160015), and the newborn's perineum or scrotum was covered with a phototherapy diaper (Foshan Baojusheng Medical Devices Co., Ltd., GB/T33280). All newborns in this study received the following treatment: continuous phototherapy for 24 hours, 6–8 hours of rest, and phototherapy for another 24 hours. The decision to continue treatment for the next 24 hours was then determined by the extent to which jaundice improved in each newborn.

3. Inclusion criteria: (1) Jaundice index, according to the phototherapy index of the American Pediatric Association, jaundice index reaches phototherapy index; (2) Newborn age ≤ 2 weeks old; (3) Gestational age between 37 weeks and 42 weeks; (4) Birth weight between 2,500 g and 4,000 g; (5) Antibiotics and ecological preparations were not used before collecting specimens; (6) The mother was healthy during pregnancy with no history of special drug use and did not take antibiotics or microecological agents before, during, or after delivery; (7) Newborns fed artificially before admission; (8) Voluntary signing of an informed consent form.

4. Exclusion criteria: (1) Gestational age < 37 weeks or ≥ 42 weeks; (2) Bilirubin level as high as the exchange standard; direct bilirubin elevation; (3) Patients with pneumonia, sepsis, or other diseases; (4) Patients with severe immunodeficiency; (5) Patients with hereditary metabolic diseases; (6) Congenital biliary malformation or other organ malformation; (7) Drug allergy; (8) According to the judgment of the researcher, it is possible to reduce the enrollment. For example, if the guardian has mental illness and the living or working environment often changes, it is easy to cause loss of follow-up.

5. Ethics: Approved by the ethics committee of Shanghai Sixth People's Hospital East Campus(Approval No:2020-071). All family members signed an informed consent form.

6. Specimen collection: Stool was collected three times: before phototherapy, 24 hours after phototherapy, and 48 hours after phototherapy; stool samples were frozen at -80°C immediately after retention. Each stool sample was ≥ 500 mg.

7. Macrogene sequencing: Intestinal probiotic flora before and after phototherapy were studied in newborn stool samples through macrogene high-throughput analysis. DNA extraction and detection: according to the instructions of the QIAamp PowerFecal Pro DNA Kit (QIAGEN, Germany), fecal DNA was extracted. Library construction and quality inspection: qualified DNA samples were randomly broken into fragments with lengths of about 350 bp by an ultrasonic breaker. The DNA library was prepared by the steps of terminal repair: adding A at the 3' end, adding a sequencing linker, purification, fragment selection, and PCR amplification. After the completion of library construction, electrophoresis and NanoDrop were used for preliminary quantification. Qubit quantification was carried out, and qPCR was used to accurately quantify the effective concentration of the library and ensure quality. Sequencing: after the quality inspection was qualified, different libraries were mixed according to the requirements of effective concentration and target off-machine data quantity. Illumina HiSeq sequencing was then performed. Bio-information analysis: sequencing data was preprocessed, starting from clean reads after quality control, then using SOAPdenovo to assemble the metagenome, and finally annotating species and analyzing abundance.

8. Metabonomics detection: Bile acids, short-chain fatty acids, and non-targeted metabolites were detected in this study. Treatment of stool samples: Add 0.3 methanol to about 100 mg of a stool sample to yield a protein precipitate, vortex for 1 minute, and centrifuge at 4℃ for 10 minutes (12,000 * g); Dilute the supernatant 10 times, vortex for 1 minute, and centrifuge at 4℃ for 10 minutes (12,000 * g). Bile acids were detected by LC/MS, short-chain fatty acids were detected by GC-MS, and non-targeted metabolites were detected

9. Statistical analysis: SPSS23 software was used for statistical analysis, and the measurement data subject to normal distribution is expressed by mean standard deviation (χ s). Multiple groups of samples are compared by variance analysis. A Kruskal-Wallis nonparametric rank sum test was used for comparison between groups that do not obey normal distribution. Count data should be expressed by frequency or percentage, and a Chi-square test should be used for comparison between groups. A Spearman rank correlation analysis was used to analyze the correlation between samples. The difference was statistically significant: $p < 0.05$.

Results

1. A total of 50 newborns participated in this study, and we obtained the basic situation of these research subjects. See Table 1.

Table 1
Basic information

Basic information of subjects (n = 50)	Mean ± SD
Gestational age (week)	38.7 ± 8.77
Birth weight (kg)	3.3 ± 0.36
Days of jaundice (day)	2.18 ± 1.40
Age (day)	7.10 ± 5.24
Phototherapy time (h)	88.51

2. The main probiotic strain present in the newborn intestinal tract is *Bifidobacterium*, along with a small amount of *Lactobacillus*. Probiotic strains changed in neonatal intestinal flora after phototherapy for 24 hours and 48 hours; *Bifidobacterium* and *Lactobacillus* decreased significantly ($p < 0.05$). See Figs. 1a and 1b. The specific changes of *Bifidobacterium* and *Lactobacillus* classification are shown in Fig. 2. Noteworthy changes took place in *Bifidobacterium animalis*, *Bifidobacterium breve*, and *Lactobacillus fermentum*, which were significantly reduced after phototherapy ($p < 0.05$).

3. In a correlation analysis between changed probiotic strains and bile acid metabolism indexes, we found *Bifidobacterium* was positively correlated with many metabolites ($p < 0.05$) such as chenodeoxycholic acid, hyodeoxycholic acid, cholic acid, allocholic acid, and β-cholic acid. *Bifidobacterium* was also negatively correlated with many metabolites ($p < 0.05$) such as glycocholic acid, sodium taurocholate, sodium TUDCA, chenodeoxycholic acid, taurocholate, and sodium taurocholate. *Lactobacillus* was negatively correlated ($p < 0.05$) with α-sodium cholate and β-cholic acid. See Fig. 3 and Table 2.

Table 2
Correlation between bile acid and probiotics

name	Positive correlation Bile acid	Correlation coefficient R	P Values	Negative correlation Bile acid	Correlation coefficient R	P Values
Bifidobacteria	CDCA	0.54	0.002	GCA	-0.50	0.005
	HDCA	0.36	0.05	THDCA + TUDCA	-0.39	0.03
	CA	0.60	0.0004	TCDCA	-0.53	0.002
	ACA	0.52	0.003	TCA	-0.67	0.001
	beta-CA	0.51	0.004			
Lactobacillus				alpha-MCA	-0.37	0.05
				beta-CA	-0.39	0.04
Bifidobacterium brevis	6-ketoLCA	0.39	0.03			
	DCA	0.39	0.04			
	6,7-diketoLCA	0.39	0.03			
	GUCA	0.39	0.03			
	GHDCA	0.39	0.03			
Bifidobacterium animalis	NorCA	0.50	0.005			

4. A correlation analysis between probiotic strains and metabolic indexes of short-chain fatty acids revealed that metabolites such as acetic acid, butyric acid, propionic acid, and caproic acid were significantly correlated with some Bifidobacteria ($p < 0.05$). See Fig. 4 and Table 3.

Table 3
Correlation analysis between probiotics and short-chain fatty acids

name	Positively correlated short chain fatty acids	correlation coefficient (r)	P Value	There was a negative correlation Short chain fatty acids	correlation coefficient (r)	P Value
Bifidobacteria	acetic acid	0.231	0.03			
Bifidobacterium Streptococcus	acetic acid	0.241	0.02			
				propionic acid	-0.29	0.007
Bifidobacterium dentin	butyric acid	0.24	0.02			
	propionic acid	0.25	0.02			
lactobacillus	acetic acid				0.02	-0.24
	Hexanoic acid	0.24	0.007			

5. After phototherapy, non-targeted metabolites in the neonatal intestinal tract changed significantly, as shown in Fig. 5. The correlation analysis between probiotic strains and non-targeted metabolites also has significant statistical significance, as shown in Fig. 6; Table 4 shows the correlation analysis of non-targeted metabolites with significant changes in probiotics.

Table 4
Correlation analysis between significantly changed probiotics and non-targeted metabolites

name	DCA	P.value	r
Bifidobacterium longum	L- Histidine monohydrochloride monohydrate	0.01	0.23
	2- Methylbutyroylcarnitine	0.02	-0.22
Bifidobacterium rhamnoides	Glucurone	0.03	-0.20
Bifidobacterium animalis	N- Acetyl-beta-D-mannosamine	0.03	-0.20
	Levonorgestrel	0.04	-0.19
Lactobacillus fermentans	Quinolinic acid	0.04	-0.19
	Glycerophospho-N-Palmitoyl Ethanolamine	0.04	0.19

Discussion

There are more than 1000 kinds of bacteria in the human intestinal tract, with microbial density increasing from the proximal to the distal intestinal tract[5]. The large intestinal microbial system has formed an inseparable symbiotic relationship with the human body. When the balance of the intestinal flora is disrupted, beneficial bacteria decrease, harmful bacteria increase, and many diseases can occur as a result[6–7]. Probiotics like *Lactobacillus* and *Bifidobacterium*[8] directly and indirectly adjust the composition of host intestinal microbes and activate host endogenous microbial groups. Because of these restorative effects, probiotics have been widely used in clinical practice. Some scholars assert that probiotics regulate intestinal flora, lower intestinal pH, reduce the quantity and activity of β-glucuronidase (β-GD), inhibit the intestinal-hepatic circulation of bilirubin, maintain intestinal peristalsis, promote bilirubin excretion, and improve feeding intolerance in patients with jaundice[9–10].

However, previous research has not reported whether the phototherapy treatment process can cause changes in probiotics. Our research found that the abundance of three types of probiotics decrease significantly after phototherapy: *Bifidobacterium breve*, *Bifidobacterium animalis*, and *Lactobacillus fermentum*. *Bifidobacterium breve* not only had the highest basic abundance; it also had the most obvious decline after phototherapy. The decrease of these probiotic strains may contribute to phototherapy side effects, and may even damage the long-term flora establishment and metabolism of children.

The relationship between intestinal microorganisms and hosts has important implications, which continue to be revealed through studies in molecular biology. For example, many small-molecule metabolites are produced by the co-metabolism of the intestinal flora and host, such as bile acid. Bile acid plays a key role in cholesterol metabolism, lipid digestion, intestinal and liver circulation, and in other regulatory pathways of human body. Intestinal flora regulates the synthesis and metabolism of bile acid, which influences the quantity and structure of intestinal flora and improves the host's immune system by regulating inflammation[11]. Dietary and intestinal microflora interact with bile acid pools, which affect the hydrophobicity, toxicity and regulation of bile acids through biotransformation reactions [12]. Cholesterol is metabolized in the liver to form conjugated bile acids, and the primary bile acids excreted to the intestine are changed by early dissociation, dehydrogenation and differential isomerization of intestinal flora to form secondary bile acids [13]. Under the action of bile salt hydrolase, produced by bacteria such as *Bifidobacterium*, *Lactobacillus*, and *Bacteroides*, combined bile acid is hydrolyzed into free bile acid[14]. Then, secondary bile acid is generated by 7α-dehydroxylation activity of bacteria like *Clostridium*, which is found in feces[15]. Therefore, intestinal flora plays an important role in the synthesis and metabolism of bile acids. Disorder of the bile acid pool caused by diseases or temporary antibiotics may lead to various disease states. Studies performed by Zampa[16] and others have confirmed that when *Bifidobacterium* and *Lactobacillus* are used by volunteers as dietary supplements, bile acid content in the feces of volunteers decreases significantly. Our study found that, except for the significant changes of probiotics, the content of deoxycholic acid increased after 48 hours of phototherapy, which was significantly correlated with *Bifidobacterium breve*. Therefore, after phototherapy for newborns with jaundice, levels of *Bifidobacterium* and *Lactobacillus* in intestinal probiotics decreased, especially *Bifidobacterium brevis*, which may have weakened their inhibitory effect on the growth of *Clostridium* in

the intestinal tract. Because the increase of *Clostridium* strengthened its dehydroxylation, the generation of secondary bile acids increased, leading to an increase of intestinal-liver circulation and reducing the effect of phototherapy itself. These findings provide a theoretical basis for administering suitable probiotics to newborns with jaundice who undergo phototherapy treatment[17–18].

In the analysis of probiotics and short-chain fatty acid metabolites, we found that many short-chain fatty acid metabolites decreased when the concentration of probiotics decreased. According to the number of carbon atoms in the carbon chain, organic fatty acids with less than 6 carbon atoms are called short chain fatty acids, mainly including acetic acid, propionic acid, isobutyric acid, butyric acid, isovaleric acid and valeric acid. Short chain fatty acids are rapidly absorbed by hindgut, which can not only store energy, but also reduce osmotic pressure. Short chain fatty acids play an important role in maintaining the normal function of large intestine and the morphology and function of colonic epithelial cells. Short chain fatty acids can also promote the absorption of sodium, and butyric acid is more effective than acetic acid and propionic acid. Butyric acid can also increase the production of lactic acid bacteria and reduce the number of Escherichia coli. Short chain fatty acids can directly stimulate the gastrointestinal tract [19], activate the secretion of motilin, promote gastrointestinal peristalsis and accelerate gastric emptying [20]. The acidic environment can increase osmotic pressure in the intestinal cavity, increase water secretion, reduce the mucus degree of feces, and facilitate defecation[21–22], thus promoting the excretion of bilirubin, reducing bilirubin levels in vivo, and relieving jaundice to some extent. Our research shows that phototherapy leads to the decrease of probiotics and associated short-chain fatty acids, which may explain some of its clinical side effects.

We found that non-targeted metabolites also changed significantly after phototherapy. Many non-targeted metabolites that are significantly correlated with the changes of probiotics after phototherapy are involved in the metabolism of nutrients in the body. For example, L-histidine hydrochloride, which is mainly used as a nutritional supplement and is a quasi-essential amino acid (i.e., an essential amino acid for infants and young children), is synthesized slowly in the human body. If a deficiency in L-histidine is found to lead to symptoms such as growth retardation and eczema, this metabolite may be positively correlated with *Bifidobacterium longum*. A non-targeted metabolite negatively related to *Bifidobacterium animalis* is N-acetyl-D-mannosamine (Mannac). Mannac is an essential precursor of N-acetylneuraminic acid (NeuAc), and the specific monomer of bacterial capsular polysialic acid (PA) is involved in the occurrence of neurological diseases. Quinolinic acid[23] has a significant negative relationship to *Lactobacillus fermentum*. Quinolinic acid is an endogenous NMDA receptor agonist, which is synthesized from L-tryptophan through the kynurenine pathway; thus, it has the potential to regulate the injury and dysfunction of N-methyl-D-aspartate neurons. The changes of probiotics caused by phototherapy may indirectly affect the metabolism of newborns through the above non-targeted metabolites.

In addition, studies[24] have shown that probiotic supplementation can shorten the phototherapy time of neonatal jaundice. Preventive probiotics can not significantly reduce the incidence of jaundice. Therefore, it is not recommended to use probiotics routinely to prevent or treat neonatal jaundice.

Conclusions

The metabolism of bilirubin in newborns is closely related to the intestinal microenvironment, and disorders in the intestinal flora can exacerbate jaundice and even affect the therapeutic effect of phototherapy. While phototherapy is a standard treatment for neonatal jaundice, it does have side effects such as fever, diarrhea, and rash. Our research found that phototherapy causes changes in neonatal flora, which may contribute to these side effects. This study focuses on the changes of intestinal probiotic strains and metabolism of newborns receiving phototherapy, and we conclude that phototherapy can significantly reduce important probiotics in the body and affect the metabolism of bile acids. There is currently no uniform probiotic selection standard for newborns with jaundice receiving phototherapy, and this study provides a theoretical basis for identifying one that alleviates side effects effectively.

Declarations

Ethics approval consent to participate

Approved by the ethics committee of Shanghai Sixth People's Hospital East Campus(Approval No:2020-071). All family members signed an informed consent form.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design of the research: FSN. Acquisition of data: ZK, ZF. Analysis and interpretation of the data: ZJP, WZM. Statistical analysis: LAP. Obtaining financing : None. Writing of the manuscript : FSN and MYN. Critical revision of the manuscript for intellectual content : FXH.

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Not applicable

References

1. Bhutani VK, Stark AR, Lazzeroni LC, Poland R, Gourley GR, Kazmierczak S, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. J Pediatr, 2013; 162(3): 477-482.
2. Faulhaber FRS, Procianoy RS, Silveira RC. Side Effects of Phototherapy on Neonates. Am J Perinatol, 2019; 36(3): 252-257.
3. LAI Y C, YEW Y W. Neonatal blue light phototherapy and melanocytic nevus count in children:asystematic review and metaanalysis of observational studies[J]. Pediatr Dermatol, 2016;33(1): 62-68.
4. Demirel G, Celik IH, Erdeve O. Impact of probiotics on the course of indirect hyperbilirubinemia and phototherapy duration in very low birth weight infants. J Matern Fetal Neonatal, 2013; 26(2): 215.
5. Sommer F, Bäckhed F. The gut microbiota-masters of host development and physiology[J]. Nat Rev Microbiol, 2013; 11(4):227-238.
6. O'Hara AM, Shanahan F. The gut flora as a forgotten organ[J]. EMBO Rep, 2006; 7(7): 688-693.
7. Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO).Guideline for the evaluation of probiotics in food[Z].2002.
8. Han X, Zhang J, Tan Y, Zhou G. Probiotics: A non-conventional therapy for oral lichen planus. Arch Oral Biol, 2017; 81: 90-96.
9. Liu PC, Yan YK, Ma YJ, Wang X W, Geng J, Wang MC, et al. Probiotics Reduce Postoperative Infections in Patients Undergoing Colorectal Surgery: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract, 2017;17: 6029075.
10. Liu W, Liu H, Wang T, Tang XQ. Therapeutic effects of probiotics on neonatal jaundice[J]. Pak J Med Sci, 2015; 31(5): 1172-1175.
11. Staley C, Weingarden A R, Khoruts A, Sadowsky MJ. Interaction of gut microbiota with bile acid metabolism and its influence on disease states[J]. Appl Microbiol Biotechnol, 2017; 101(1): 47-64.
12. Small DM, Rapo S. Source of abnormal bile in patients with cholesterol gallstones[J]. N Engl J Med, 1970, 283(2): 53-57.
13. Sagar NM, Cree IA, Covington JA, Arasaradnam RP. The Interplay of the Gut Microbiome, Bile Acids, and Volatile Organic Compounds[J].Gastroenterol Res Pract, 2015; 3(3): 398585.
14. Ridlon JM, Harris SC, Bhowmik S, Kang DJ, Hylemon PB. Consequences of bile salt biotransformations by intestinalbacteria [J]. Gut Microbes, 2016; 7(1): 22-39.
15. Yusof R M, Haque F, Ismail M, Hassan Z.Isolated of Bifidobacteria infantis and its antagonistic activity againt ETECO157 and Salmonella typhimurium S-285 in weaning foods[J]. Asia Pac J Clin

Nutr, 2013; 9(2):130-135.

16. Zampa A, Silvi S, Fabiani R, Morozzi G, Orpianesi C, Cresci A. Effects of different digestible carbohydrates on bile acid metabolism and SCFAproduction by human gutmicro-flora grown in an in vitro semi-continuous culture[J]. Anaerobe, 2004; 10:19-26.
17. Zhou S, Wang Z, He F, Qiu HX, Wang Y, Wang HH, et al. Association of serum bilirubin in newborns affected by jaundice with gut microbiota dysbiosis[J]. J Nutr Biochem, 2019; 63: 54-61. DOI:10.1016/j.jnutbio.2018.09.016.
18. Zhang K, Fan SN, Lv AP, Ma YN, Fang XH, Zhang JP. Integrated Analysis of Microbiota with Bile Acids for the Phototherapy Treatment of Neonatal Jaundice. J Pediatrics, 2020;under review.
19. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Cavallo L, Francavilla R. The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal motility in preterm newborns[J]. J Pediatr, 2008;152(6): 801-806.
20. Armanian AM , Barekatain B , Hoseinzadeh M , Salehimehr N. Prebiotics for the management of hyperbilirubinemia in preterm neonates[J]. J Matern-Fetal Neo M, 2016; 29(18): 5.
21. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Cavallo L, Francavilla R. Effects of probiotic and prebiotic on gastrointestinal motility in newborns[J]. J Physiol Pharmacol, 2009; 60(Suppl 6): 27-31.
22. Indrio F, Riezzo G, Raimondi F, Francavilla R, Montagna O, Valenzano ML, et al. Prebiotics improve gastric motility and gastric electrical activity in preterm newborns[J]. J Pediatr Gastr Nutr, 2009; 49(2): 258-261.
23. Guillemin GJ. Quinolinic acid: neurotoxicity. FEBS J. 2012 ; 279(8): 1355.
24. Deshmukh J, Deshmukh M, Patole S. Probiotics for the management of neonatal hyperbilirubinemia: a systematic review of randomized controlled trials. J Matern Fetal Neonatal Med. 2019;32(1):154-163.

Figures

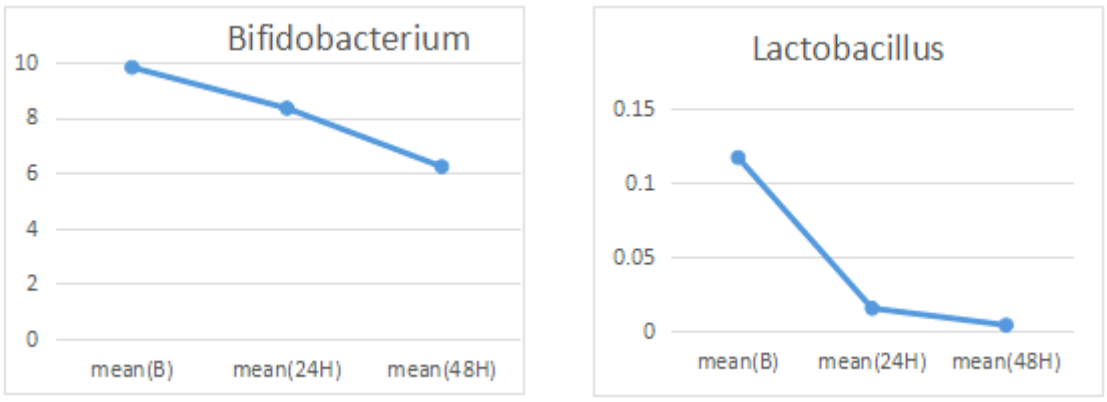

Figure 1

Changes of Bifidobacterium and Lactobacillus after phototherapy

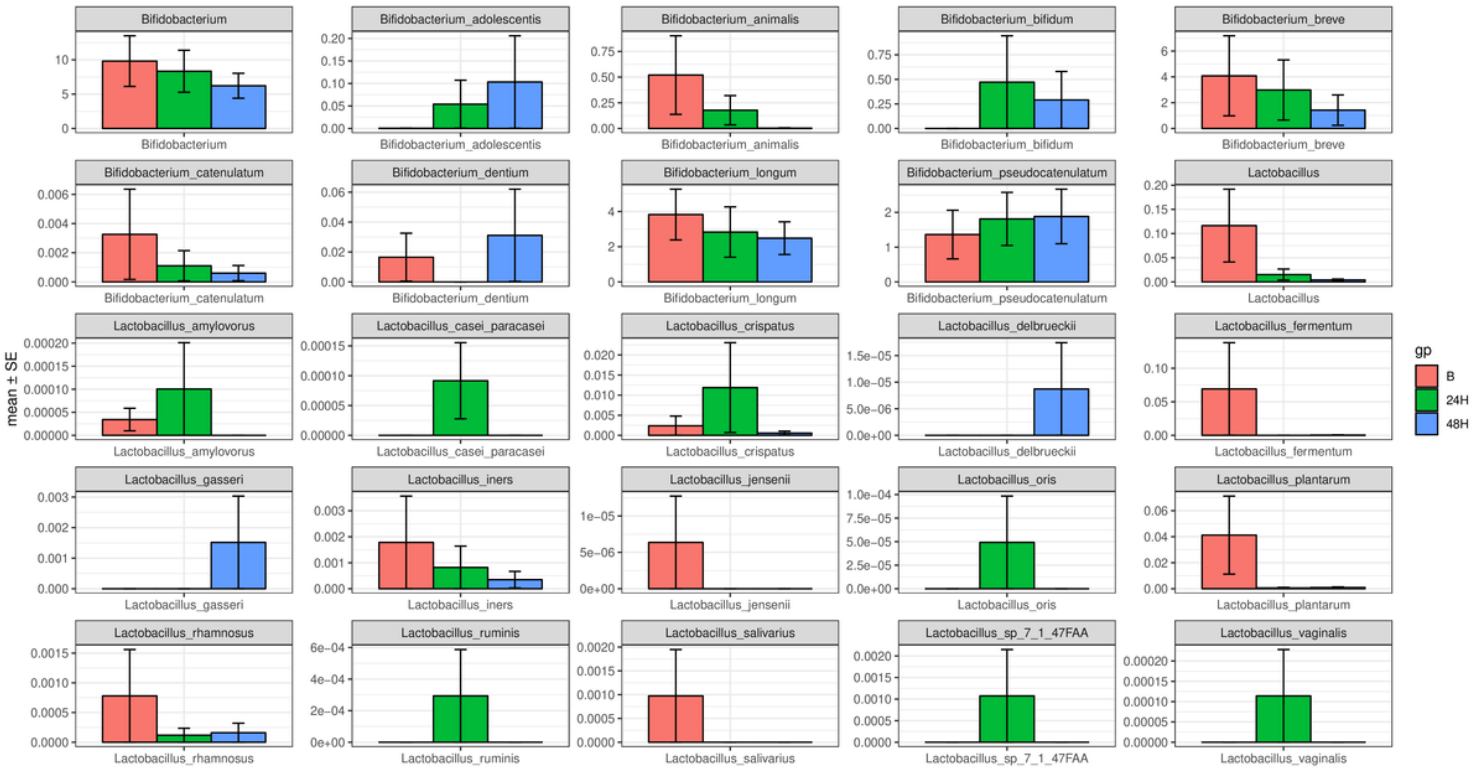

Figure 2

Different Bifidobacterium and Lactobacillus strains change after 24 hours and 48 hours of phototherapy

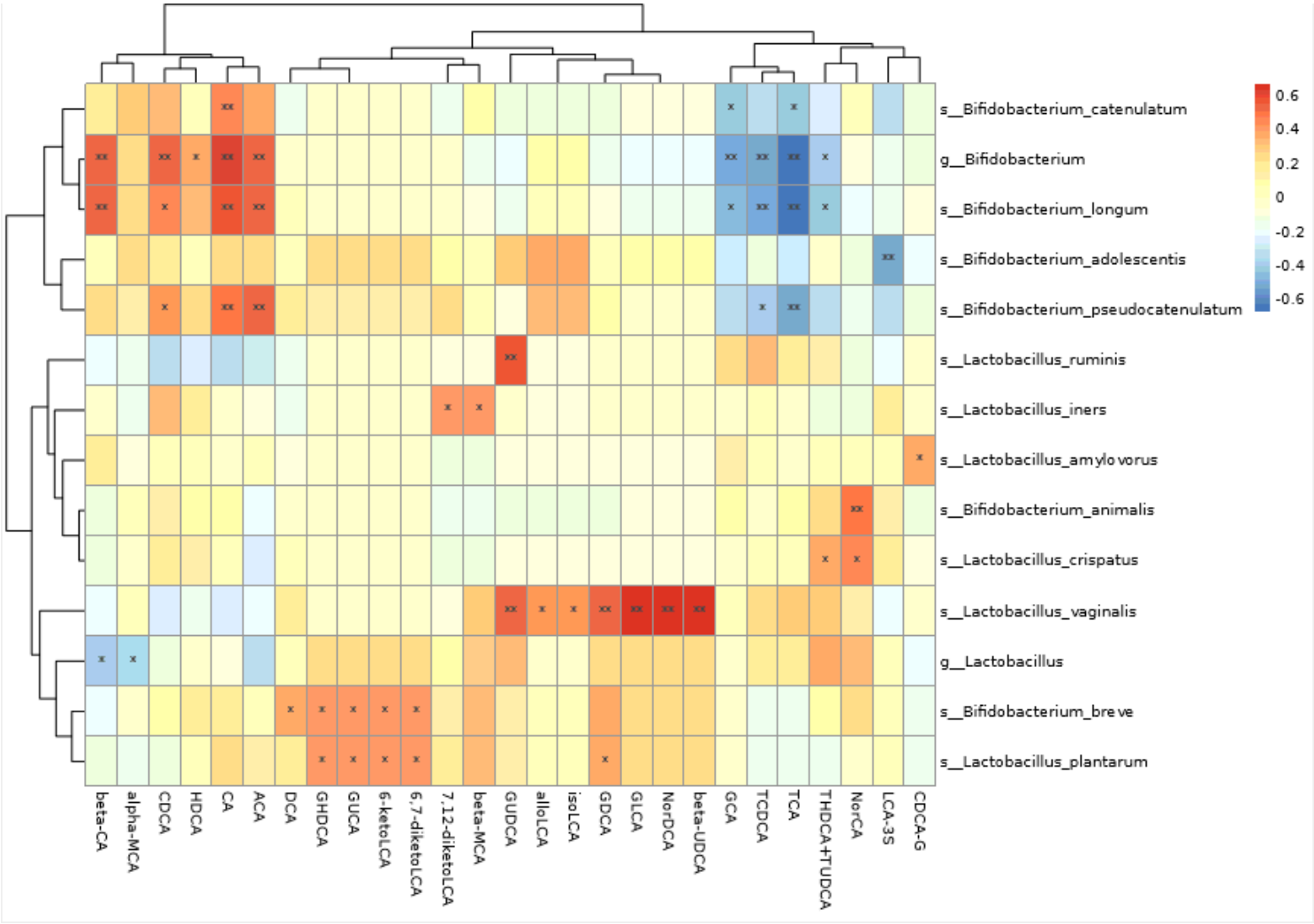

Figure 3

Correlation analysis between probiotic strains and bile acid metabolism indexes

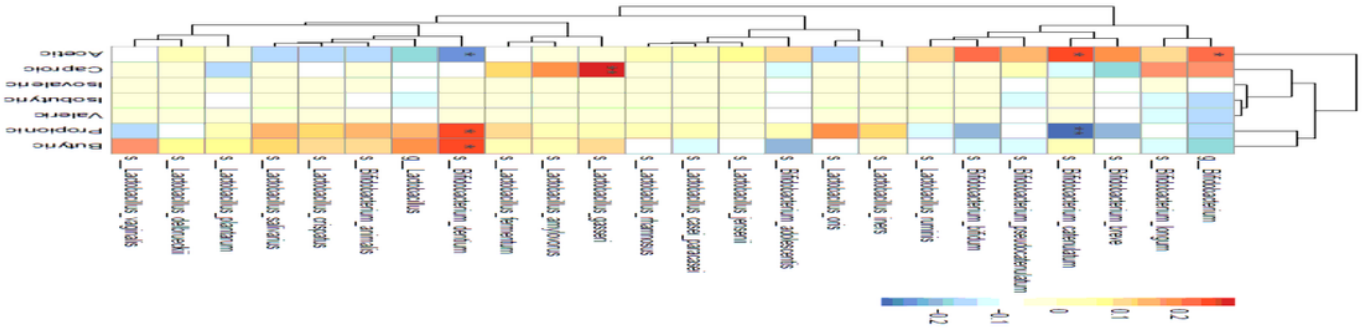

Figure 4

Correlation analysis between probiotics and short-chain fatty acids

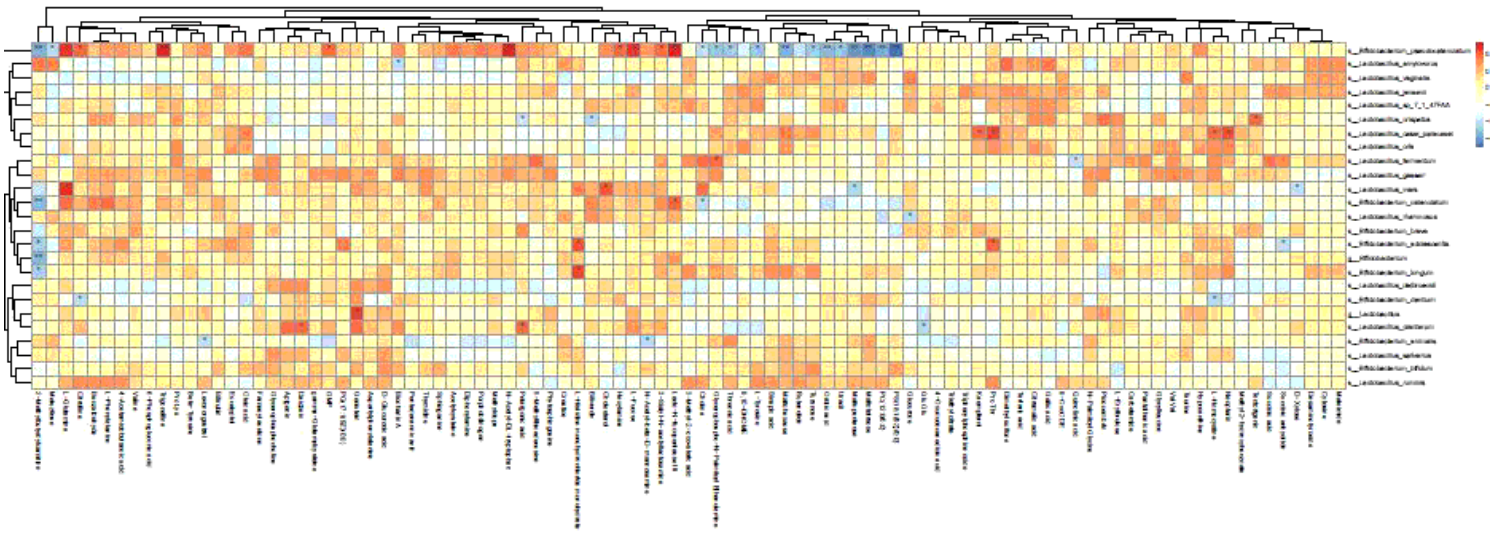

Figure 5

There are significant differences in non-targeted metabolites caused by different phototherapy time (1, 2 and 3 represent before phototherapy, 24 hours after phototherapy and 48 hours after phototherapy, respectively)

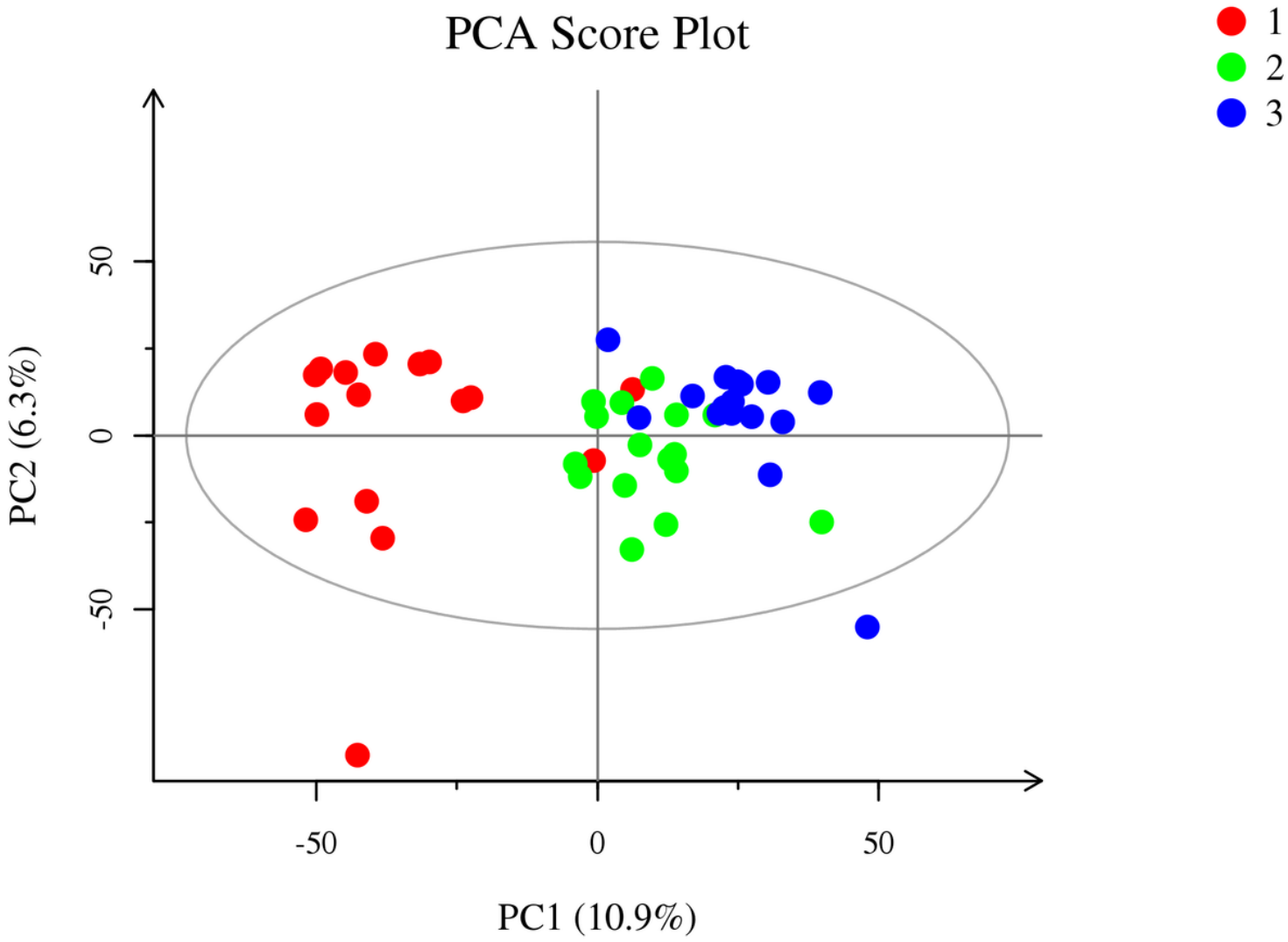

Figure 6

Correlation analysis between changed non-targeted metabolites and probiotic changes